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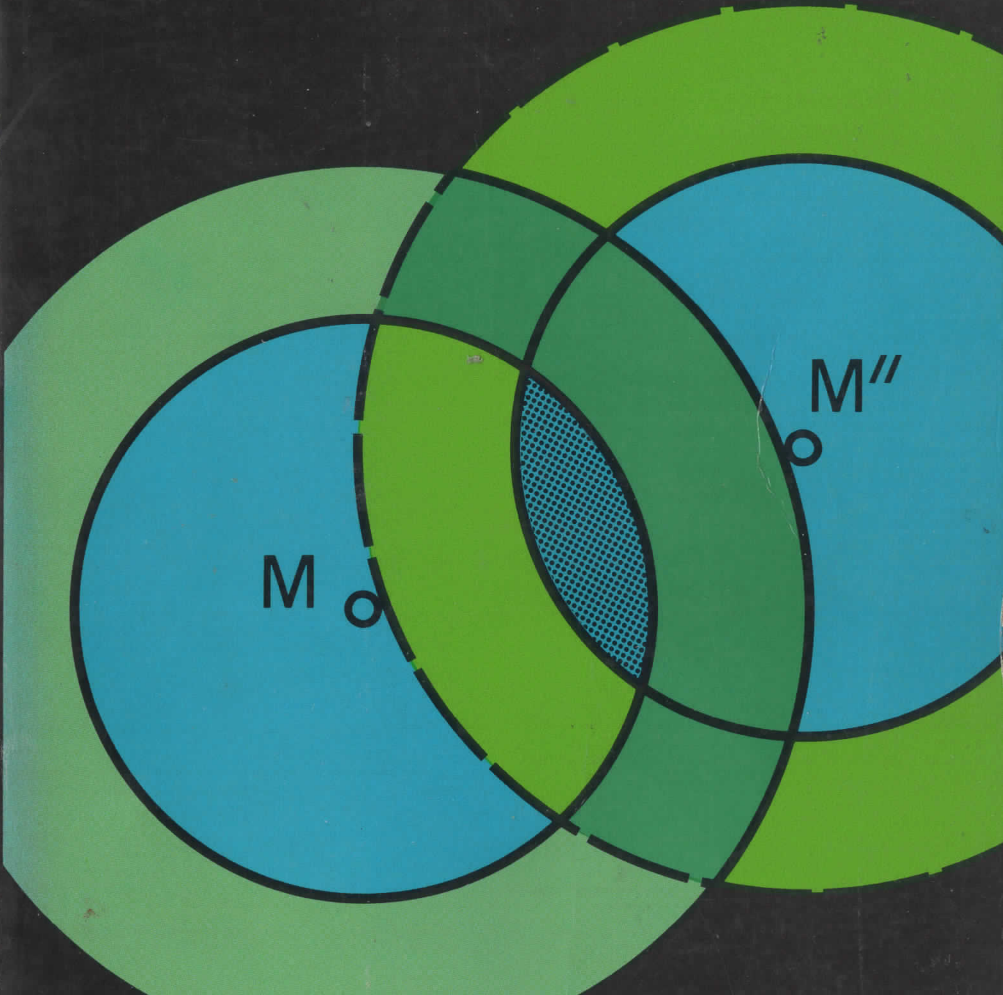
GENETIC HOMEOSTASIS



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but to weigh and consider.
BACON

GENETIC HOMEOSTASIS

BY

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Professor at the University of California in Berkeley

DOVER PUBLICATIONS, INC.
NEW YORK

Published in Canada by General Publishing Company, Ltd., 30 Lesmill Road, Don Mills, Toronto, Ontario.

Published in the United Kingdom by Constable and Company, Ltd., 10 Orange Street, London WC 2.

This Dover edition, first published in 1970, is an unabridged and unaltered republication of the work originally published by Oliver and Boyd, Edinburgh and London, in 1954.

Standard Book Number: 486-62506-0
Library of Congress Catalog Card Number: 78-99761

Manufactured in the United States of America
Dover Publications, Inc.
180 Varick Street
New York, N.Y. 10014

To

EVERETT R. DEMPSTER

ACKNOWLEDGMENTS

IT is a pleasure to express my gratitude to the John Simon Guggenheim Memorial Foundation (Henry Allen Moe, Secretary-General) for a Fellowship which enabled me to undertake the preparation of this work; to Professor Adriano Buzzati-Traverso for the hospitality of the Institute of Genetics at the University of Pavia, where the major part of the writing was done; to Professor Vittorio Tonolli and Dr Livia Pirocchi Tonolli for their gracious welcome at the Istituto Italiano di Idrobiologia in Pallanza, where the work was finished; to Dr Giovanni E. Magni whose indefatigable efforts on my behalf made my stay in Italy instructive and pleasant beyond all expectation; to Dr Renzo Scossiroli for the preparation of the figures and his aid in many other ways. The manuscript has been read by Professor Buzzati-Traverso and by Dr Hugh P. Donald, to whom I am indebted for many valuable suggestions. The latter has also been exceedingly kind in lending his critical hand editorially and in providing facilities for some of the clerical work.

I.M.L.

January–July 1953
PAVIA AND PALLANZA

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PART I

INTRODUCTORY

1. HOMEOSTASIS

One of the most important contributions made by Walter B. Cannon to the field of physiology was the development and elaboration of the concept of physiological homeostatis. He has defined homeostasis as the totality of steady states maintained in an organism through the co-ordination of its complex physiological processes. By extension it may be said that homeostasis refers to the *property* of the organism to adjust itself to variable conditions, or to the self-regulatory mechanisms of the organism which permit it to stabilize itself in fluctuating inner and outer environments.

The idea of balance as a necessary condition for the preservation and perpetuation of life is an ancient one, and has been traced by Cannon, at least in its primitive form, to the time of Hippocrates. Undoubtedly, the early notions on the subject tended to view homeostatic mechanisms from a crude vitalistic standpoint. It is to the richly deserved credit of Cannon and his followers that this apparently mysterious and mystical property of biological organisms has been reduced to terms of interactions between constituent parts and functions. Needless to say, final answers to the problems of physiological homeostasis are by no means available. Indeed, the origin of biological feedback mechanisms is in itself a question of central interest in the study of evolution. Their existence is recognized, the largely mechanistic basis of their operation is accepted, but their increasingly complex development from the lower to the higher forms of life still presents the focal problem of evolution of adaptations. That physiological homeostasis is essentially the fundamental adaptation was recognized even before the term was coined, for, as Claude Bernard (quoted from Haldane, 1932) stated three-quarters of a century ago, 'all the vital mechanisms, varied as they are, have only one object, that of preserving constant the conditions of life in the internal environment'.

In the epilogue to his book on *The Wisdom of the Body* Cannon (1932) considered the analogy between homeostasis of the body physiological and the body politic. Just as in the former auto-regulating stabilizing processes are essential for survival, so must they operate in the latter. And again one may readily see that social homeostasis is an adaptation developed by societies in existence at any time. When the institutions that make up a society are subjected to strains with which their homeostatic mechanisms can no longer cope the society disintegrates. The nature of the adaptations and the specific types of stresses to which they are subjected are, of course, incommensurate at the two levels, but the functional principle involved is very probably the same.

The step that Cannon took from the organismal to the social level by-passed some intermediate stages. One of them, for instance, with reference to human societies, is the psychological level, and the psychologists have not been remiss in studying it (e.g. Stagner, 1951). Another one is ecological homeostasis (Allee *et al.*, 1949), and still another, of significance to the subject of evolution, is that of an interbreeding group, whether a species or a more restricted Mendelian population is considered. It is self-regulation at this level which will be considered here and which may be designated as *genetic homeostasis*. This phenomenon can be defined as the property of the population to equilibrate its genetic composition and to resist sudden changes. It is very probably the same property as the *genetic inertia* of Darlington and Mather (1949).*

The suggestion that this phenomenon is interjacent between its physiological and social counterparts is not merely a pigeonholing device. It actually bridges the gap between the specific types of mechanisms operating at the two extremes. Thus it correlates with physiological homeostasis in the sense that the adaptive properties of the individual (physiological in general and developmental in particular) contribute to and determine the adaptive properties of populations (genetic). It correlates with social homeostasis in the sense that both are time-binding, operating between, rather than within, generations. It is the inter-generation lag that permits the evolution of new social adaptations; it is the inter-generation lag that is the basis of genetic adaptation of a population.

Again, just as the psychologist can now study the physico-chemical bases of the processes involved in their types of homeostasis, just as, one may hope, the sociologist will be able to formulate laws of growth and development of societies in terms stripped of irrational and supernatural constructs, so the geneticist has at his disposal a series of mechanistic (not necessarily in the crudest sense of the word) processes which can be invoked in explanation of genetic homeostasis. These processes are basically reducible to the phenomena of Mendelian inheritance and of gene action.

The following pages contain an essay developing this thesis. It is proposed to demonstrate that Mendelian populations possess self-regulating properties, to establish a connexion between genetic and developmental homeostasis, to suggest that heterozygosity provides a basis for both phenomena, and to consider some consequences of these points for evolution and breeding.

The idea of homeostasis of individual organisms as a goal of evolution is, of course, not original (see Muller, 1950*a*, for reference to the genetic, and Waddington, 1948, to the developmental, aspects). Similarly, the notion of self-stabilizing properties of populations has been previously advanced by, among others, Schmalhausen (1949). The relationship between individuals and populations was also brought out earlier by Mather (1943*a*). The genetic model for homeostasis described here is not unlike the one suggested in a very schematic way by Penrose (1948). Thus the framework of the discussion to follow rests upon ideas expressed by earlier students of the subject. Nevertheless, there are many points of difference in emphasis and formulation between what has been said before and what will be said here. They arise from the fact that the writer's primary orientation is that of a worker in animal improvement rather than that of a naturalist. As a consequence, the considerations presented are limited to those below the macro-evolutionary level and do not include problems of speciation or such phenomena as the replacement of cross-fertilization as a breeding system by self-fertilization. Further, they lean heavily on evidence from artificial selection and from domestic animals, biological material which unfortunately has not been fully exploited by students of evolution in the post-Darwinian era.

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* The term *genetic* homeostasis occurred to me in the course of a discussion with Dr H. P. Donald and others, and made its first appearance in print (Lerner, 1950) a year after *genetic inertia*. I am reluctant to yield priority to the designation of Darlington and Mather because inertia in the physicist's sense does not in any way convey the concept of auto-regulation.

2. THE GENERAL HYPOTHESIS

DOBZHANSKY (1951*a*) has defined a Mendelian population as 'a reproductive community of sexual and cross-fertilized individuals which share a common gene pool'. One of the salient features of this spatio-temporal entity is an integrated structure which endows it with properties transcending those of its individual members. Older evolutionary theories have tended to consider Mendelian populations as relatively uniform, with reserves of variability carried as recessive mutants at individually low frequencies. The major process of evolutionary significance was presumed to consist of successive substitutions at each locus of alleles less advantageous to an individual by more advantageous ones. More recently justification has been obtained for the replacement of this idea by that of dynamic variability of the genetic composition of populations, lending emphasis to the concept of evolution as 'an irregularly shifting state of balance' (Wright, 1950). This change of outlook has caused the integrative properties of populations to assume paramount importance in evolutionary thought, not only for problems dealing with differentiation between populations, but with an even greater force for those relating to genetic phenomena within populations.

It seems obvious that properties of populations, as much as properties of individuals, have evolved under the action of natural selection. At the same time it is not immediately clear as to how natural selection operating on the individual level could lead to the development of integrating factors at the level of populations. Many students of evolution (e.g. Fisher, 1932; Simpson, 1941) have stressed the fact that natural selection cannot be concerned with properties of units higher than the individual (except in cases of inter-group selection, such as may be found in insects; see Haldane, 1932). The evolution of the integrative characteristics of Mendelian populations must have occurred under this view as a by-product of individual selection. The simplest example of this situation is found in the Hardy-Weinberg equilibrium. It is meaningless to attribute to individuals this property of large populations, whereby in the absence of selection, mutation or migration they tend to maintain their genetic composition constant. Yet it is the Mendelian behaviour of the units of inheritance linking individuals of successive generations that endows the population as a whole with this characteristic.

Evidence for more complex attributes of Mendelian populations has gradually accumulated as a result of descriptive and experimental studies in population genetics. It calls for explanation, provisional though it may be, if a clearer understanding of evolutionary processes and a better genetic control of populations of domestic plants and animals is desired. Furthermore, it is more than likely that some of the various phases of population behaviour, studied independently of each other by many investigators, are aspects of a single, more general, phenomenon. In the present work it is proposed to review a series of superficially unconnected observations on the genetics of populations, to present a unifying hypothesis to account for them, and to demonstrate that it is possible to construct a genetic model on the basis of which the more complex integrative properties of Mendelian populations can emerge from evolutionary forces operating on individual genotypes.

The three types of evidence which contribute most heavily to the theory advanced refer to:

1. data on artificial selection in instances where deceleration of gains is observed or a plateau is reached without apparent reduction in genetic variability;
2. observations on phenotypic deviants which are sporadic and ubiquitous for a given species, but which fail to exhibit clear-cut Mendelian inheritance;
3. estimates of environmentally determined variability of homozygotes and heterozygotes.

Other types of evidence, which contribute to the problem but which will be considered here in less detail include:

1. inbreeding degeneration;
2. balanced polymorphism and, more generally, instances of selective advantage of heterozygotes;
3. the general superiority in fitness of phenotypic intermediates.

Following the presentation in a summary form of the substance of the general hypothesis advanced on the basis of these points, an examination of the evidence itself will be undertaken. Genetic models underlying the theory formulated will be then presented, and the inferences that can be drawn from them discussed.

The main theses suggested may be listed in broad outline as follows:

1. The evolution of cross-fertilized organisms has effected genotypes producing developmental patterns with a considerable degree of self-regulation. In embryological terms the process of development of specific form has become canalized, leading to a uniformity of phenotypic expression in individuals of a given population, in spite of the genetic variability between them.

2. Mendelian populations are also possessed of self-equilibrating properties tending to retain a genetic composition that produces a maximum average fitness in the particular environments in which these populations exist.

3. The most likely mechanism for both types of homeostasis lies in the superiority with respect to fitness of the heterozygous over the homozygous genotypes:
(*a*) ontogenetic self-regulation (*developmental homeostasis*) is based on the greater ability of the heterozygote to stay within the norms of canalized development;
(*b*) self-regulation of populations (*genetic homeostasis*) is based on natural selection favouring intermediate rather than extreme phenotypes.

4. Acceptance of these premises leads to the conclusion that evolution of auto-regulation has established levels of obligate heterozygosity in Mendelian populations. The selective advantage of multiple heterozygotes because of their better buffering, and hence smaller deviation from the phenotypic optimum for fitness, operates on the level of individuals. But it is the very same mechanism which permits the population to meet the two requirements for successful existence:
(*a*) uniformity of adaptive phenotypic expression to avoid excessive reproductive waste; and
(*b*) genetic variability to protect the population from systematic and non-systematic changes in the environment.

5. Sporadic occurrence of abnormal morphological deviants (*phenodeviants*) is caused by the intrinsic properties of multigenic Mendelian inheritance, due to which a certain percentage of individuals of every generation falls below the threshold of the obligate proportion of loci needed in a heterozygous state to ensure normal development. The biology of these characters (some homoeotics in *Drosophila*, skeletal and other abnormalities in rodents, crooked toes in chickens, and many other traits) is the biology of inbreeding degeneration.

6. The inheritance of metric traits may be considered, at least in an operational sense, to be based on additively acting polygenic systems, while the totality of traits determining reproductive capacity and expressed as a single value (fitness) exhibits overdominance.

7. Attempts to shift populations too rapidly and too far from adapted mean values for specific traits, either by artificial selection or by changes in the breeding system, are counteracted by natural selection which is directed towards the maintenance of a phenotypic balance between fitness-determining characters. This behaviour is a product of the previous evolutionary history of the population. The resistance of natural selection can be overcome when new balanced combinations based on the utilization of free genetic variability arise.

The theoretical justification of these points may be best deferred until the material on which they rest is examined. A considerable amount of evidence available is universally known and does not call for a detailed review. Accordingly only the points of immediate reference to the hypothesis expounded are emphasized in the following sections. Furthermore, it should be stressed that the hypothesis developed is applicable only to populations with genetic systems based exclusively on cross-fertilization. The selection pressures to which organisms of other types are subjected may be of an entirely different nature and do not enter to any extent into the present discussion.

PART II

EVIDENCE

3. SELECTION RESULTS

THE literature on responses of populations to selection for metric traits is extremely abundant. There are instances in which selection was not effective, those in which continued progress has been obtained for a large number of generations, and those in which selection progress was arrested by partial exhaustion of genetic variance. The present discussion, however, will be confined to the type of response which is of critical significance to the problems under consideration, i.e. to cases in which a period of genetic gains is followed by a plateau, which in turn is succeeded by a further response to selection. The most elaborate example of this type is represented by the prolonged experiments for changes in the number of abdominal chaetae in *Drosophila melanogaster* carried out by Mather and Harrison (1949).

A schematic representation of some of their data on selection for a higher number of bristles is given in Figure 1. It may be seen that selection was extremely effective for some 20 generations. At this point the reduction in reproductive capacity which accompanied selection response became so great that, in order to keep the population in existence, selection had to be suspended. After several generations the unselected population stabilized itself at a chaeta number higher than that in the original population.

From the population propagated without artificial selection pressure for several generations a new selected line was established. Without further difficulties due to reduction in fecundity, it was possible to reach a higher average bristle number than in the first selection phase, a number which stayed under continuous selection pressure at a plateau level. Suspension of selection at this point produced only a slight regression in bristle number, the population maintaining itself at the new level without resumption of artificial selection. A further response was obtained in the continuously selected line after a period of some 50 generations without change in the number of chaetae.

It is not necessary for our purposes to discuss the details of this experiment, for which the reader may be referred to the original publication and to such analyses of the authors' interpretation as, for instance, the one made by Wright (1952). It is sufficient to note the factors which have the most important bearing on the hypothesis outlined in the previous section. They include:

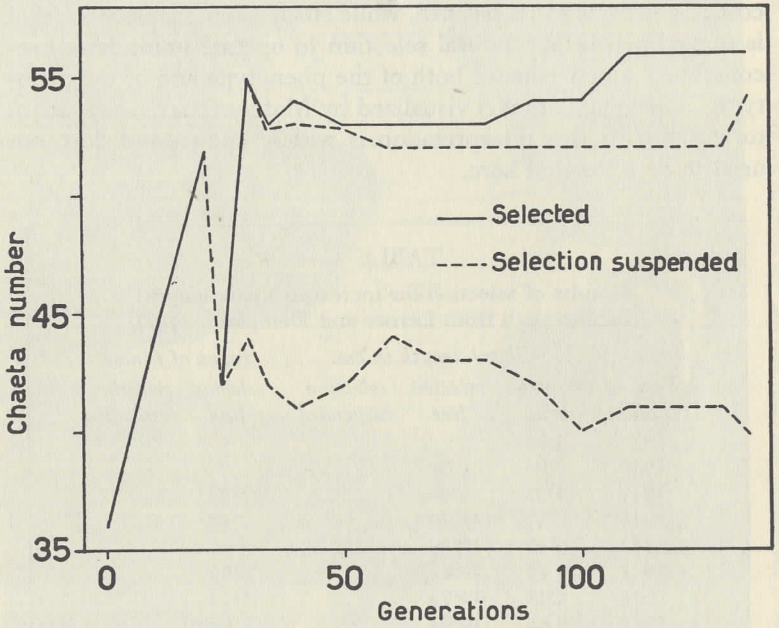


FIGURE 1. Schematic representation of the results of selection for a high number of abdominal chaetae in *Drosophila melanogaster* (from Mather and Harrison, 1949)

(*a*) the establishment under the pressure of selection of different optimal chaeta numbers, as judged by the equilibrium values reached after selection was suspended;

(*b*) the reduction in fitness observed in the period of rapid gains, and the recovery in fitness with the suspension of artificial selection;

(*c*) the response obtained in the selected line after many generations at a plateau value.

These points suggest that the genetic elements, to which control of chaeta number can be referred, form part of an equilibrated system maintained by natural selection, which produces phenotypically balanced individuals (i.e. ones in which the phenotypic expressions of various traits are in such relation with each other as to lead to maximum fitness). Selection gains are obtained at the cost of destroying this balance, while suspension of selection (that is to say, permitting natural selection to operate unhindered) reconstitutes a new balance both of the phenotype and of the genotype. The genetic model visualized by Mather (1941, 1943, 1949) to account for this interpretation is widely known and does not need to be reiterated here.

TABLE 1

Results of selection for increased shank length (data to 1949 from Lerner and Dempster, 1951)

	Shank length in cm.			*Index of fitness*	
Year of hatch	*control line*	*selected line*	*selection suspended*	*selected line*	*selection suspended*
1938	9·69				
1939	9·62	9·92			
1940	9·55	9·92		4·67	
1941	9·37	10·20		4·47	
1942	9·46	10·29		3·56	
1943	9·42	10·46		4·63	
1944	9·41	10·73		2·48	
1945	9·48	10·84		2·62	
1946	9·44	10·71		3·09	
1947	9·77	10·73		1·57	
1948	9·89	10·96		2·22	
1949	9·53	10·78		3·12	
1950	9·58	11·10		2·54	
1951	9·59	11·08	10·86	1·63	1·33
1952	9·66	10·99	10·60	0·96	2·27

Another experiment, on a scale commensurate with the biology of the material used, has been reported by Lerner and Dempster (1951). It referred to selection for increased shank length in chickens, and *mutatis mutandis* gave the same results as the *Drosophila* work described. Table 1 shows the pertinent information (with addition of data collected since the publication of the

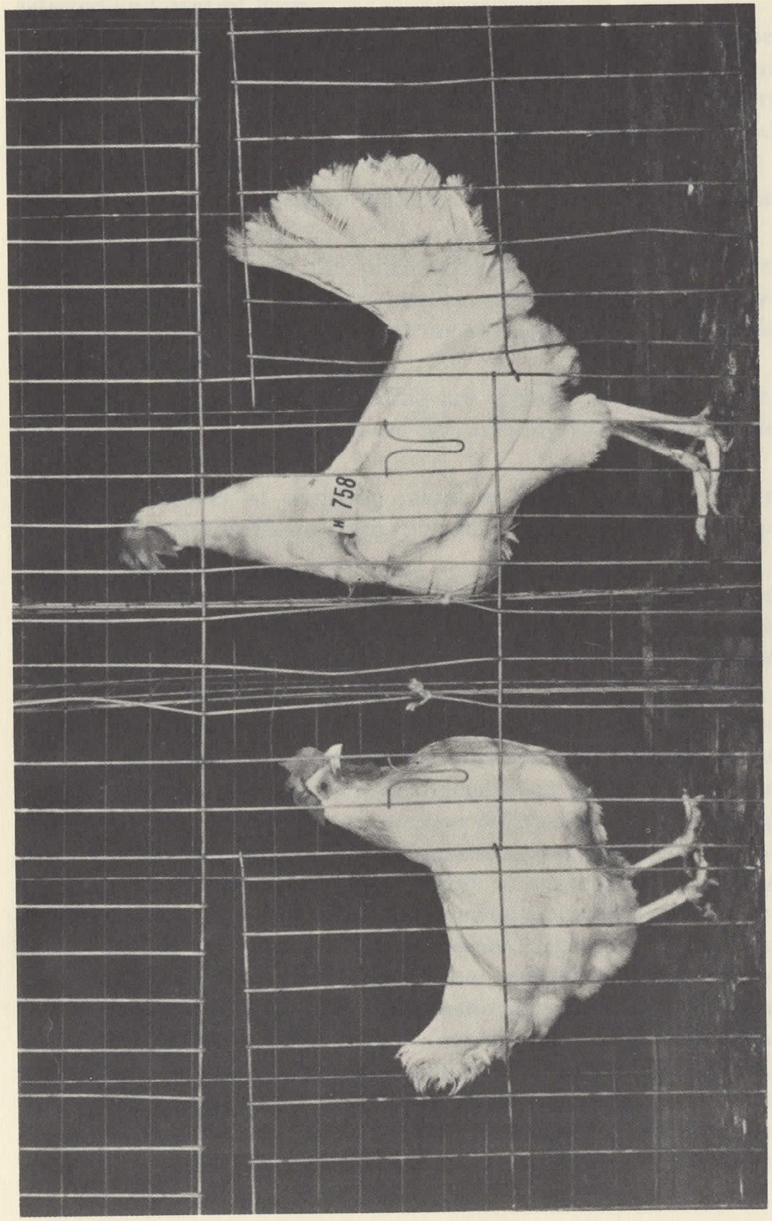
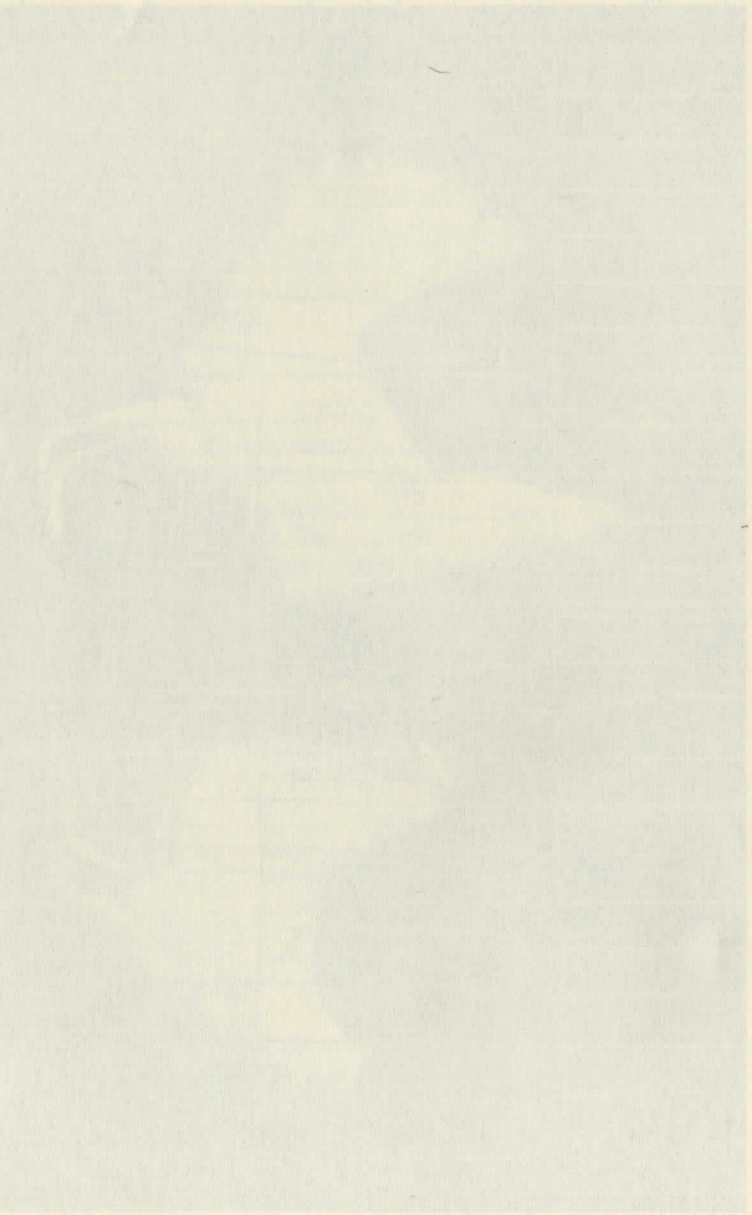


FIGURE 2. Representative females of the control line (left) and the line selected for long shank (right)



original report). Figure 2 shows representative females of the selected and control lines.

The conclusions of the original analysis, supplementary to those already listed for the report of Mather and Harrison, were based on the comparison between the first phase of the experiment, when selection was effective, with the second phase when a plateau had been reached. Those of immediate significance are:

(*a*) the amount of genetic variance in the two phases was the same (0·059 vs. 0·062);

(*b*) the proportion of the phenotypic variance attributable to additively acting genetic differences, i.e. the degree of heritability, in the two phases was the same if no correction for inbreeding is made (0·260 vs. 0·269);

(*c*) if corrections for inbreeding are applied to these figures, the heritability in the first phase was notably lower than in the second (0·287 vs. 0·410);

(*d*) the number of offspring raised to maturity per dam (an index of fitness) declined from 3·75 for the first to 2·47 for the second phase;

(*e*) no correlation between the shank length of the selected female parents and the number of offspring they produced was found in the first phase, but a negative correlation between these variables appeared in the second phase.

The procedure used to establish the last point deserves explanation. To quote from the original publication: 'If we consider the birds selected as parents of the next generation in any year we can readily compute the *expected selection differential* by subtracting from their average shank length the average of their own generation. If we weight the shank length of these females by the number of their offspring which survived until the time of measurement, the weighted average obtained would represent the *realized selection differential*. The ratio of the realized to the expected selection differential provides a measure of association between fitness and shank length. If it is less than unity, it means that among selected birds those with longer shanks produce, on the average, fewer offspring than those with shorter shanks. This would provide a strong indication that natural selection for fitness does indeed operate in the opposite direction from artificial selection for longer shanks.'

For the first phase of the experiment, when selection gains were being obtained (change per year 0·188 cm.), the ratio was 0·94. For the second phase, when a plateau was reached (change per year −0·007 cm.), the ratio dropped to 0·77. Furthermore, when instead of the phenotype an estimate of the genotype was used for each dam (based on the average shank length of her full sisters), the respective ratios for the two periods were found to be 0·98 and 0·68. It would thus seem that, whereas in the first phase natural selection played a minor rôle in the changes in shank value, in the second phase it became an effective antagonist to artificial selection. Theoretical computations presented by Lerner and Dempster indicate that some 70 per cent of the difference between the gains obtained in the first and in the second phase can be accounted for by this mechanism. Of this amount, 0·50 refers to natural selection between families of full sisters, and 0·20 to that within families of full sisters.*

From point (*c*) above it may be argued that natural selection discriminated against the relatively more homozygous individuals. The correction for inbreeding apparently was far too great if it is considered that heritability remained constant throughout the experiment. It should be noted that this supposition (over-correction for the coefficient of inbreeding) is in agreement with the conclusions of Düzgüneş (1950), who found that the more heterozygous individuals in inbred lines of chickens have a greater likelihood of surviving to maturity.

The general picture emerging from results of such selection experiments suggests that Mendelian populations carry within them heterozygous genetic reserves sufficient to produce, under artificial selection, shifts in the mean values of metric traits of the order of several standard deviations. These reserves are apparently maintained by natural selection, which, at the outset, does not interfere with artificial selection. When, however, the changes exceed what may be called tolerance limits, extreme deviates fail to reproduce themselves as efficiently as the individuals closer to the original mean of the population. An antagonism is thus induced between artificial and natural selection. Further, a population kept at a plateau level by the balance of these two opposing

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* It may be noted that in the experiments on mice of Falconer (1953) and of Falconer and King (1953) no antagonism between artificial and natural selection pressures was noted. However, because of the selection method used, only the second type of effect (within families) was to be expected.

pressures may eventually break through the ceiling by utilization of whatever new free genetic variability becomes available through mutation or crossing-over.

The new genetic variation is not necessarily specific for the metric trait under selection. It may represent variability in the residual genotype, which is brought into a new balanced phenotypic relation with the changed mean for the selected character. It should also be noted that natural selection in at least some cases does not depend on competition between individuals. In the shank-length experiment the greatest elimination of offspring of long-shanked birds occurred because of their failure to hatch. No direct competition could be involved either at the time of elimination or even at the time of deposition of eggs.

We shall return to the genetic basis of these results in subsequent sections. At this point it may be well to consider the more general evidence on the part played by selection in maintaining a balance between phenotypic traits,—a significant phenomenon for the interpretation now proposed.

4. BALANCED PHENOTYPES

The best adapted individuals in a population are those which exhibit a harmonious combination of all characters leading to maximum fitness. Natural selection working on the whole complex of traits will then tend to favour either organisms clustering around mean values for all characters (see e.g. Fisher, 1930), or those in which extreme deviations for one trait are compensated for by some form of deviation in another. As Wright (1951) has stated, 'the best adapted form in a species is usually one that is close to the average in all quantitatively varying characters'. The intermediate values towards which selection is directed are not static, but represent optima which may change with changes in genetic frequencies (Fisher, 1932). When mean values of particular characters move in one direction, there may be compensatory movements in others. For preserving a balance specific genes may be necessary (Haldane, 1932). To achieve the balance between different characters, extreme phenotypic deviants must be produced, only to be sacrificed to natural selection (Schmalhausen, 1949).

An example of elimination of the extremes is provided by the frequently quoted observations of Bumpus (1899) on the survival of sparrows after a violent storm. The average deviation from the mean for 8 out of the 9 body measurements taken was smaller for the survivors than for the birds which perished. Similarly, Weldon (1901) found that the elimination of landsnails between young and old stages led to a decrease of variability around the average peripheral radius of the shell. More recently, Hecht (1952) demonstrated the mechanisms of natural selection for intermediate size in the West Indian lizard, *Aristelliger praesigrus*, whereby extremely large and extremely small animals were eliminated. In domestic poultry Lerner (1951) has shown that the highest reproductive fitness was found in birds with a genotype for an intermediate egg size, and that the optimum in populations subjected to artificial selection for larger size of eggs fell below the mean of the population. Other examples of differential elimination of extremes are provided in the studies of di Cesnola (1907) on Helix shells, of Karn and Penrose (1951) on human birthweights, and of Rendel (1943) on duck eggs. Reference to the latter investigation was inadvertently omitted in Lerner's (1951) survey of data on the subject.

Less direct evidence of balance is available from descriptive ecological data on the relationship between various morphological and physiological traits in natural populations. As a single example, the situation in three sympatric species of Peromyscus described by McCabe and Blanchard (1951) may be referred to. These populations have characteristically different numbers of young produced per female (6, 9 and 20). It is obvious that these differences must be compensated for by some factor, such as differential longevity, if the populations are, as they seem to be, in equilibrium with respect to number of individuals. In laboratory populations conditions for a similar balance in reproductive behaviour may be found. Thus Sawin and Curran (1952) note a multiplicity of partly independent components of reproduction (functional gonads, normal accessories, endocrines, egg capacity, milk production, maternal behaviour, growth, viability) in different lines of rabbits. These must be in balance with each other for successful existence of a population.

Experimental evidence for compensating types of balance is not lacking. Thus Robinson (1951), in attempting to increase the lamb crop by means of endocrine therapy, found that injection of pregnant mare serum into breeding ewes at the appropriate time in the oestrous cycle produced multiple ovulation. The average number of fertile eggs per control animal was less than 2, while for ewes injected with 2000 units of pregnant mare serum it was 16. However, by the 21st day of pregnancy the number of living foetuses was respectively 1·47 and 1·67, while the number of eventually surviving lambs in the two groups was 1·33 and 1·27 per ewe mated. It seems clear that the overall physiological organization of the sheep, reflecting the total genotype, limits the number of eggs shed to one not much different from the number of young which the uterine environment is capable of supporting. Should mutations equivalent in their effect to that of the injected material have arisen, the reproduction rate would not have increased until the residual genotype caught up, so to speak, with the new situation.

A further instance, this time dealing with growth rate, can be cited. From the data of Bailey (1952) and those of Rutman (1951) it appears that inbred lines of rats exhibit a negative genetic correlation between the growth-promoting quality of milk and the rate of growth of the young in the post-weaning period. It is not unreasonable to interpret this situation in terms of adaptive values of adult size. With superior milk the young reach at weaning a weight which, if it continued to increase proportionately, would carry them above the optimum size. Hence when the quality of milk is high, selection is directed towards a relatively low post-weaning growth rate. Conversely, inferior milk produces somewhat smaller weanlings, so that selection here is for rapid post-weaning growth. Similarly the genotype for growth rate may determine the direction of selection for milk quality. Thus the over-all effect is to establish a balance between the two types of growth-rate determinants. A similar inference can be drawn from the data on swine described by Dickerson and Grimes (1947).

In general, existence of negative genetic correlations between traits subjected to selection may be interpreted as evidence for genetically determined balance between phenotypic characters. The problem, however, is somewhat complicated by two facts. Firstly, it appears that, when the characters involved are direct components of fitness (e.g. the number of eggs produced and hatchability in birds, where competition between embryos does not exist, as it does in the previously cited instance in sheep), the correlation under selection has been shown, at least in one case, to be positive (Lerner and Dempster, 1951). Secondly, processes under similar physiological control might be expected to be positively correlated, as for example is found to be the case for gains obtained in different stages of growth of pigs (Hazel, Baker and Reinmiller, 1943) or of cattle (Knapp and Clark, 1947). Nevertheless, there are examples available where genetic correlations of a negative type can be demonstrated. Particularly convincing are the instances in which the phenotypic correlation is positive (e.g. that in the relation between thickness of belly and thickness of back fat in pigs, noted by Johansson and Korkman, 1950, or in a number of wool characters in sheep, reported by Morley, 1951), since genetic changes between generations in one character in a given direction will be accompanied here by changes in another character in a different direction.

What is meant by phenotypic balance has been probably made clear by the examples cited. Multiplication of these would not serve any useful purpose. Instead we may next turn to a review of some evidence which suggests that intermediate and balanced phenotypes are in many cases based on heterozygous genotypes.

5. SELECTIVE ADVANTAGE OF HETEROZYGOTES

It is not meant to imply in the present discussion that heterozygosity is the sole mechanism by means of which balanced phenotypes are produced. Models for intermediate phenotypic optima based on epistatic interaction have been constructed (Wright, 1935*a* and *b*; Lush, 1945), and there is also evidence for the rôle of epistasis in determining viability (Wallace *et al.*, 1953). Non-additiveness of this type does not preclude the existence of loci, blocks, or chromosome segments which in a heterozygous state contribute to the production of balanced phenotypes. It is this aspect of the situation that has particular bearing on the hypothesis under discussion, and which is to be considered here.

As a first step, it seems necessary to establish the fact that, theoretical objections to the contrary (see sections 13 and 20), there are enough instances of heterozygotes with selective advantage to warrant generalizations about the rôle played by heterozygosis in the adaptation of populations. Secondly, it must be shown that such advantages are attained by heterozygotes because they lead to better balanced phenotypes.

Although unequivocal evidence of polygenic overdominance in fitness (of particular importance on the basis of considerations set forth in section 20) is scarce, there are a number of instances that can be cited in which single genes and chromosome segments exhibit this property. The present section is devoted to a review of these cases. It should be pointed out, however, that heterosis in crosses between non-interbreeding populations, and examples in which heterozygotes show an increase in some metric measurement over homozygotes, are of no particular significance in the context of our discussion. The cases of interest to us are those in which heterozygote superiority is reflected by increased fitness. To accept this distinction one does not need to follow the terminology proposed by Dobzhansky (1952) to distinguish *heterosis* from *luxuriance*. For present purposes it is the selective advantage of heterozygotes in a Mendelian population that is of immediate significance, rather than the property of overdominance in crosses with respect to any given morphological trait. Indeed the hypothesis proposed here suggests that the assumption that individual metric characters manifest additive gene behaviour in their inheritance is consistent with overdominance of the totality of their expression in terms of fitness.

The fate of a mutation in a population depends on the properties of its homozygote and heterozygote expressions. A dominant mutation, if unfavourable, will be eliminated fairly rapidly. A recessive one under the same circumstances will remain in a population in a low frequency. A favourable mutation, if it is dominant, will largely replace the original allele, while, if it is recessive, it will do so completely. In all cases the balance between mutation and selection pressures will determine the exact gene frequency at equilibrium. The important point is that contributions to the variance of a polygenically determined trait by loci, at which gene frequencies are near the extreme values, will be small.

Where the heterozygote is at a selective disadvantage, the equilibrium point of gene frequency will be 0·5 if the two homozygotes are exactly equal in selective value, and close to zero for the inferior allele when they are not. The frequency of occurrence of the first of these situations will depend on how often mutations with an additive selective value exactly equal to the original form will arise.

Finally, there may be mutations which in the heterozygous state have a higher selective value than either homozygote. Here the equilibrium point for the frequency of gene A is $q_A = \frac{1-k}{1-2k}$, where k represents the coefficient of selection in the following notation describing the relative reproductive rates of the different genotypes:

$$\begin{array}{ll} AA & 1 \\ Aa & 1\text{-}ks \\ aa & 1\text{-}s \end{array}$$

In the alternative notation where the reproductive rates are

$$\begin{array}{ll} AA & 1\text{-}S \\ Aa & 1 \\ aa & 1\text{-}T \end{array}$$

the equilibrium point q_A is $\frac{T}{S+T}$ while $q_a = \frac{S}{S+T}$.

The value of k is of course, negative. Thus q_A can have a range from approximately 1·0 to the lower limit of 0·5, depending on the magnitude of k (or in the second notation on the difference between S and T). The smaller the difference in selective value between AA and aa relative to that between Aa and AA, the closer will the equilibrium value of q_A approach 0·5, and the greater will be the contribution of the locus to the variance.

Thus, even if mutations having an advantage as heterozygotes are relatively rare, they are of the kind which persist in a population (a fact which was realized early in the history of population genetics, see e.g. Fisher, 1922) and, what is of particular importance, they contribute most to the population variance. The same reasoning may be extended from genes with single phenotypic effects to those with pleiotropic properties each of which individually exhibits dominance, to polygenic blocks in which the superiority of the heterozygote may result from simple dominance of component genes, and to the even more complex situation where long chromosome segments are maintained as inversions.

The greatest amount of experimental evidence on the selective advantages of heterozygotes is provided for the latter case by the studies of Dobzhansky and his collaborators (see Dobzhansky, 1951*b*, for literature citations) on *Drosophila pseudoobscura*. In this species, the evidence appears to be clear that individuals heterozygous for third chromosome inversions have a selective advantage over homozygotes. An even more extreme situation is found in

D. subobscura, in which obligate heterozygosity for inversions is apparently the rule (Buzzati-Traverso, 1952).

The evidence on higher adaptive values of single gene heterozygotes (this may, of course, include pseudoalleles) has not been as extensively elaborated as that for *D. pseudoobscura*. Nevertheless, a variety of examples may be found in the literature (for earlier references see Ford's summary, 1945, on balanced polymorphism). Thus, in *D. melanogaster*, Buzzati-Traverso (1952) records the existence of a light-eyed mutant maintained in nature by a selective advantage of its heterozygous form. In the same species, *ebony* and *sepia* appear to have a higher fitness in a heterozygous state than have their normal alleles (Kalmus, 1945; Teissier, 1947*a* and *b*). Similarly, da Cunha (1949) found a body colour mutant in *D. polymorpha* endowed with the same property. Other examples are provided by a mutant in the grouse locust (Nabours and Stebbins, 1950), and by at least three *D. melanogaster* lethals (among 75 tested) with a heterozygous survival advantage found by Stern *et al.* (1952), whose report includes literature references to earlier cases of a similar kind.

The small proportion of lethal mutants possessed of this property in the experiment of Stern *et al.* is not a strong argument against the occurrence of heterozygous superiority in natural populations. In the first place, the experiment dealt with lethals, where the difference between survival values of the two homozygotes is at the maximum instead of the minimum (as noted above, the case of greatest contribution to variance in fitness). In the second place, the mutants investigated are not necessarily representative of those persisting in natural populations.

In connexion with the last point it should be noted that evidence of such persistence is not in itself an adequate demonstration of the superiority in fitness of heterozygotes. There are instances in which the maintenance of alternative alleles in nature depends less on this factor than on a cyclic seasonal reversal of selective values of the two homozygotes, such as may be the case in *Adalia bipunctata* (Timofeeff-Ressovsky, 1940*b*) and in the hamster (Gershenson, 1945). Indeed, it is difficult to establish without experimental tests whether one or the other or both conditions (superior fitness of heterozygous individuals and seasonal reversal of fitness values of the homozygotes) are involved. Thus in the *Drosophilae* in which maintenance of inversion types is characteristic of wild populations, differences in behaviour exist between species and between populations of the same species. Seasonal cycles of frequency of inversion types are found in *D. funebris* in urban but not in rural areas (Dubinin and Tiniakov, 1945). In *D. robusta*, in the absence of regular cycles of inversion-type frequencies, seasonal variation of morphological traits can be discerned (Stalker and Carson, 1949). In another population of the same species, seasonal changes in inversions are found in males but not in females (Levitan, 1951). *D. persimilis* shows no cycles, while some populations of *D. pseudoobscura* do and others do not (Dobzhansky, 1948*a*).

This complication is responsible for the fact that the studies in which the physiological basis of heterozygote superiority has been identified are of such great importance. These include Caspari's (1950) investigation of the gene affecting testis colour in *Ephestia kühniella*, in which overdominance in fitness is produced by dominance of two pleiotropic effects (the 'complementary dominance' of Whiting, 1951), and that of Spiess, Ketchel and Kinne (1952) on the greater egg-laying capacity of inversion heterozygotes in *D. persimilis*. Less compelling for our purposes is the observation that *glossy/spectacle* heterozygotes of *D. melanogaster* have higher fitness than either homozygote recessive (Green and Oliver, 1951), because the wild-type homozygote is clearly superior to the compound. On the other hand, an exceedingly convincing demonstration of the point to be made is given by the case in which overdominance in fitness of inversion types of *D. pseudoobscura* arose under selection either of the genic contents of the inversion types themselves, or of modifiers (Dobzhansky and Levene, 1951).

In populations of domestic animals, rather strong indications of a selective advantage of heterozygotes for genes determining the production of blood antigens in chickens was found by Shultz and Briles (1953). As a rule, it may be rash to conclude from evidence on artificial selection of domestic animals that heterozygotes are more fit in the Darwinian sense than are homozygotes. It is possible that a heterozygote may have a phenotypic expression for some trait which approximates more closely to the breeder's ideal than do the homozygotes, and thus is permitted to leave more offspring. The simplest examples of this sort are Blue Andalusian chickens and Palomino horses, in which the heterozygote expression of respective single loci represents the breed standard. Other possible examples include the lethals *hypotrichosis* and *acroteriasis* in Swedish Holstein-Friesians (Wriedt, 1930), achrondroplasia in the Dexter, Telemark and other cattle breeds (Brandt, 1941), a series of dwarf conditions in beef cattle (Gregory *et al.*, 1951), and muscular hypertrophy (Kidwell, 1952) in the same animal.

However, with respect to the blood-group of chickens it is more likely that a real advantage in fitness is involved since (*a*) selection in the flock studied by Shultz and Briles was based on egg production, a component of fitness, rather than on any morphological criteria, and (*b*) at least at one locus, fixation under close inbreeding failed to occur in a number of lines studied.

A somewhat similar case, which deserves mention here largely because it is not well known except to poultry geneticists, is that of the Wyandotte breed. The White variety has a rather low reproductive fitness when compared with other commercial breeds of fowl (Hutt, 1940). The breed standard requires a rose comb, but a considerable proportion of single-combed birds appears in most flocks. These two facts suggested to Cochez (1951) that a lethal gene is associated with the rose-comb gene *R*. Whether or not this is the correct interpretation, it seems rather likely, as Cochez points out, that the persistence of single-comb segregates may be accounted for by some form of selective advantage of the heterozygote.

We may summarize the situation by quoting Dickerson's statement (in Craft *et al.*, 1951) regarding the rôle of heterozygosity in populations of domestic animals, since it is equally applicable to populations in nature:

'Most genes (or linked groups) affect many different vital processes and stages of development, some favourably, some unfavourably. Selection has established at intermediate frequencies only those genes (or complexes) whose favourable effects are expressed and whose deficiencies or unfavourable effects are unexpressed in the heterozygous state. Genes at intermediate frequencies contribute more to genetic variability than genes approaching fixation or elimination, and hence account for a major portion of the observed hereditary variation in total performance. Homozygotes lack the favourable effects of the alternative alleles and selection favours heterozygotes over either of the alternative homozygotes.'

We may next proceed to a brief consideration of the corollary of heterozygous superiority in fitness, i.e. inbreeding degeneration.

6. INBREEDING DEGENERATION

There is no particular need to discuss here the details regarding the reduction in fitness and viability occurring under inbreeding. Firstly, the deterioration of populations subjected to continued consanguineous mating represents a generally known phenomenon. Secondly, it may have explanations independent of the one advanced here (e.g. a simple unmasking of deleterious recessive mutants). However, some mention of the effects of endogamous mating is necessary, particularly to demonstrate that degeneration upon inbreeding is largely found in traits connected with fitness. The best evidence on the subject is from domestic and laboratory animals and plants, and it is to the first of these that we shall turn for our material.

The deleterious effects of inbreeding were discovered empirically long before the elaboration of the mechanism of Mendelian heredity. Darwin (1868, quoted from the 1894 edition) stated that 'it is a law of nature that organic beings shall not fertilize themselves for perpetuity', and attributed the recognition and development of this principle for plants to Andrew Knight and to Kölreuter. Inbreeding was considered to lead to loss of vigour and fertility, and, in more general terms, to a decline in fitness. The evidence that this situation generally occurs in domestic animals is overwhelming, in spite of the fact there are species (e.g. mice) in which brother × sister matings can be carried on indefinitely with relative impunity. The full collation of the facts bearing on this point would strain the limits of a work of monumental proportions. Hence, only a sampling of data reported or summarized for different species will be given here.

An instance of pre-Mendelian experimentation is the study of inbreeding in rats by Ritzema Bos (1894) carried on for some 30 generations. It is difficult to estimate the closeness of inbreeding achieved in this experiment since the matings were apparently not made in a systematic fashion. However, since both parent × offspring, and brother × sister matings were utilized within the closed populations which originated from a single pair of animals (a wild male and a tame albino female), it seems reasonable to suppose that a considerable degree of consanguinity was gradually attained.

The data supplied by Ritzema Bos indicate that fitness was affected by an increase in the number of unfruitful matings, by a decrease in litter size, and by a rise in the mortality of the young, as shown in the following table:

Year	*Percentage of matings without young*	*Average litter size*	*Percentage mortality to 4 weeks of age*
1887	0	7·50	3·9
1888	2·6	7·14	4·4
1889	5·6	7·71	5·0
1890	17·4	6·58	8·7
1891	50·0	4·58	36·4
1892	41·2	3·20	45·5

It is doubtful whether the actual degree of homozygosity attained was as high as that computable from the pedigrees, since considerable room for a differential survival (natural selection) of homozygotes and heterozygotes was afforded by the high degree of sterility and mortality. The effects of inbreeding on fitness, nonetheless, are obvious even in the absence of controls.

Turning to another species, the guinea pig, we have the elaborate records of the long-term investigation carried out in the U.S. Department of Agriculture by a succession of workers from Rommel to Wright, and eventually analysed by the latter (1922*a*, 1922*b*). This experiment involved a total of some 34,000 animals, including a series propagated by brother × sister matings for more than 20 generations.

The results are again typical of both earlier and subsequent studies in showing the decline in vigour under inbreeding, as well as its restoration upon crossing inbred lines. The precise details are too extensive to be reported here, but some indication of the magnitude of the observed effects is given by the regressions appearing in Table 2.

The extent of decline in fitness and its components is probably underestimated in these figures, because (1) of the 23 families originally started on the brother × sister plan of mating, 8 became extinct in the course of the experiment (probably as a result of decreased fitness), and (2) the last $3\frac{1}{2}$ years of the experiment were confined to 5 families, 4 of which were the highest of all families with respect to the number of young per year they produced, the fifth one being approximately average. Thus the data cited here refer to the superior rather than to the average inbred families.

The observed decline in fitness might be ascribed to environmental rather than to genetic causes. Although the behaviour of control non-inbred lines gives some support to this notion, Wright in his analysis has clearly demonstrated that at least a share of the degeneration in fitness was due to inbreeding. It may be seen from Table 2 that all components of fitness declined (as shown by the negative signs of the regression coefficients). The total effect on fitness, as measured by the number of young alive at weaning time, was considerable. Although only approximations on the basis of linear regressions can be made, it would seem that the number of young produced per litter declined from 12·09 in 1906 to 6·79 by 1920. The number weaned alive shows an even greater proportional decline in this period—from 9·83 to 4·29.

TABLE 2

Linear regressions of traits listed on year of inbreeding (x) in Wright's (1922*a*) guinea-pig experiment

Size of litter	2·885 − 0·043x
Litters per year	4·210 − 0·110x
Number of young per year . . .	12·092 − 0·450x
Percentage born alive	88·27 − 0·29x
Percentage of liveborn raised to weaning .	92·10 − 1·04x
Percentage of all born raised to weaning .	81·30 − 1·16x
Birth weight of young raised, in gms. .	86·17 − 0·19x
Gain from birth to weaning, in gms. .	163·70 − 1·96x
Weight at weaning, in gms. . . .	249·87 − 2·15x

The precision of these figures is not at issue. It seems clear, however, that with such a high level of loss between fertilization and attainment of breeding age considerable scope for intra-uterine and postnatal selection is available, just as in the experiment of Ritzema Bos. In general, when artificial selection for maintenance of vigour is practised concurrently with inbreeding, differential elimination of genotypes can play a major rôle. This fact is amply illustrated by the rat experiment of King (1918-19).

The remarkable features of this experiment (brother × sister inbreeding accompanied by selection for vigour) may be summarized as follows:

1. Litter size was not affected by inbreeding, if anything showing a gain to the 25th generation of inbreeding. Even more remarkable is the fact that the litter size from a given dam was the same irrespective of whether her mate was a brother or an unrelated animal.

2. Environmental conditions varied through the years of the experiment, but outbred quasi-controls contemporary with the inbreds were inferior to the latter with respect to body weight.

3. The selection intensity practised was not particularly high (468 first litters having been produced from 6825 individuals in 25 generations).

4. The coefficients of variability of body weight increased in general with inbreeding, in the extreme case of one line rising from 3·0 for the 7–15 generations to 12·9 for the 16–25 generations.

Thus it seems that in rats (and in mice, judging from the large number of inbred lines carried in different laboratories) a sufficient amount of selection pressure for vigour can be applied to overcome the deleterious effects of inbreeding. However, the question arises, as in the previously considered cases, whether the actual homozygosity under these circumstances corresponds to the computed homozygosity. In other words, it is not clear whether consanguineous mating has really led to the increases in homozygosity expected on theoretical grounds. For instance, one of the two lines that King tested after 102 generations of brother × sister mating was still heterozygous, as judged by intolerance of intra-inbred-line skin transplants (Loeb, King and Blumenthal, 1943).

On strictly Mendelian considerations continued brother × sister mating should lead to values of inbreeding coefficients not far removed from the computed ones, even if elimination of zygotes is high. That is to say, under this system of mating heterozygosity can be enforced by natural selection only at a few loci. In spite of this fact, some doubts may be and have been expressed (e.g. by Gowen, Stadler and Johnson, 1946) as to whether the theoretical basis underlying the computations of inbreeding coefficients is completely valid. No categorical judgment on this question seems possible at this time.

When we turn to inbreeding studies on domestic animals, the general agreement is that the primary consequence of consanguineous mating is a reduction in fitness. Thus Robertson's (1949) analysis and summary of experiments on dairy cattle reveals that the main effects are:

1. appearance of manifestations of recessive genes,

2. decrease in birth weight and possibly mature size,
3. increased early mortality,
4. decline in yield of milk and fat,
5. increase in sterility.

Similarly, the major effect of inbreeding in poultry (summarized by Hutt, 1950) is found to be in the reduction of hatchability. While variable results were obtained in such traits as maturity, egg production, and so forth, the reduction in fitness through hatchability was universal and marked. Düzgüneş (1950) in particular investigated the decline in fitness under inbreeding, coming to the conclusion that:

(*a*) although other stages in the life cycle may be involved in decreasing the number of offspring surviving to breeding age, hatchability is the main factor implicated, and

(*b*) offspring elimination 'appears to operate to some extent in a selective manner, so that the relatively more homozygous individuals are represented in the population at breeding age to a lesser extent than the more heterozygous ones.'

TABLE 3

Effects of inbreeding on litter size and body weight in swine (Dickerson, Lush and Culbertson, 1946)

Character	*Age in days*	*Inbreds*	*Crosses*	*Decline for each 10% inbreeding*
Litter size . .	0	6·6	7·2	0·26
	21	3·8	5·3	0·35
	56	3·5	5·1	0·37
	154	3·0	4·8	0·39
Body weight, gms.	0	2·8	2·8	0·02
	21	11·0	11·7	0·07
	56	28·1	31·7	0·90
	154	119·0	144·0	6·80

The numerous results obtained with swine again demonstrate a similar phenomenon (e.g. Willham and Craft, 1939; Comstock and Winters, 1944; Stewart, 1945). Table 3 from Dickerson, Lush and Culbertson (1946) lends considerable support to their conclusion that 'results indicate that in the development of inbred lines more careful selection is necessary to maintain litter size and viability than to hold rate of growth'. This in general seems to be the constant refrain of the workers with swine, though it has been

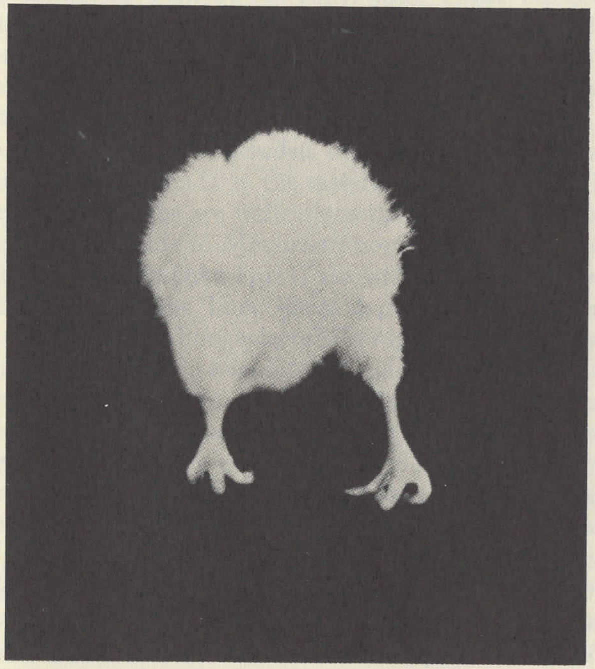

FIGURE 3. White Leghorn chick with crooked toes

found possible to maintain litter size if the rate of inbreeding is sufficiently slow to allow rigorous selection (e.g. in the report of Winters *et al.*, 1948). In these cases it is more than likely, in spite of the reservation we have already expressed, that the actual increases in homozygosity do not correspond to the computed ones (see Mather and Hayman, 1952).

Finally, the results with sheep also indicate that the traits not directly connected with fitness suffer little under inbreeding as compared with such as are (thus body weight is affected, while the type of face covering is not, in the reports of Hazel and Terrill, 1946, of Terrill, Sidwell and Hazel, 1948, and the earlier work of the same authors).

In general it may be concluded that successful propagation of domestic animals depends on the maintenance of a certain level of heterozygosity. There are indications that the obligate nature of heterozygosity extends to Mendelian populations in general. For instance, when Borissenko (1941) attempted to select *D. melanogaster* for viability, the lines selected in the low direction lost genetic variance. The lines selected for high viability, on the other hand, maintained their variability, as judged by potentialities for reversing the direction of selection. On a somewhat anecdotal level we also have the instructive story from the lips of Isaac Hershey, as cited by Anderson (1944). Hershey, a Pennsylvania corn breeder, was famous for the development of the Lancaster Surecropper, a variety which later became an important source of hybrid germplasm. Using mass selection of ears with occasional introduction from other varieties, he produced a high-yielding strain, which, however, lacked uniformity. When, under customer pressure, he started selecting for uniformity, he lost yield. For whatever it is worth, this testimony suggests that genetic variability is an important condition for yield and, therefore, in a self-perpetuating population of corn, for fitness.

7. CROOKED TOES IN CHICKENS

Since the discovery and elaboration of Mendelian laws the interpretation laid on the degenerative effects of inbreeding has tended to refer to the specific gene contents of the inbred organisms rather than to any mystical powers of inbreeding itself. Thus, when under continuous consanguineous mating, lethals, monsters or a series of defects are encountered, it is assumed that recessive genes for such abnormalities were present in the initial populations. Inbreeding presumably permitted their phenotypic emergence by increasing the probability of occurrence of homozygotes. This interpretation is basically valid, having been experimentally verified in many instances. Such verification is obtained by subsequent isolation of the offending genes and establishment of their Mendelian behaviour.

Heritable complexes and syndromes have also been found, either upon inbreeding or of spontaneous occurrence, whose expression could not be ascribed to the action of definite gene-pair differentials. Grüneberg, in a recent review (1952*a*) and discussion (1952*b*) of characters of this kind, suggested, following the majority of earlier investigators, that the inheritance of such abnormalities rests on multiple genes with various degrees of penetrance and a threshold mechanism of expression. This is probably as much as can be said for traits occasionally found in laboratory stocks. However, some characters of this type, widely spread in natural populations, in laboratory strains, and in populations of domestic animals and plants, are susceptible to the interpretation that their appearance is connected with balancing mechanisms in Mendelian populations based on heterozygosis and thus related to the phenomena of inbreeding degeneration. In the current and following sections the genetic behaviour of some illustrative examples of these characters will be described, while in later sections devoted to discussion, arguments for this interpretation will be presented.

Dubinin (1950), in his work on mutants for various abnormalities found in natural populations of *Drosophila* (Dubinin *et al.*, 1937), has termed the traits discussed here *abnormal polymorphs*. Since *polymorphism* has been defined specifically as 'the occurrence together in the same habitat of two or more distinct forms of a species in such proportions that the rarest of them cannot be maintained by recurrent mutation' (Ford, 1945), it may be somewhat confusing to use this appellation for multigenic traits. It is hence suggested that individuals manifesting abnormal phenotypes of the kind under discussion be referred to as *phenotypic deviants*, or, in brief, following the custom of Greek-Latin hybridization accepted in the best biological circles, *phenodeviants*.

Two typical cases of phenodeviants will be considered here in

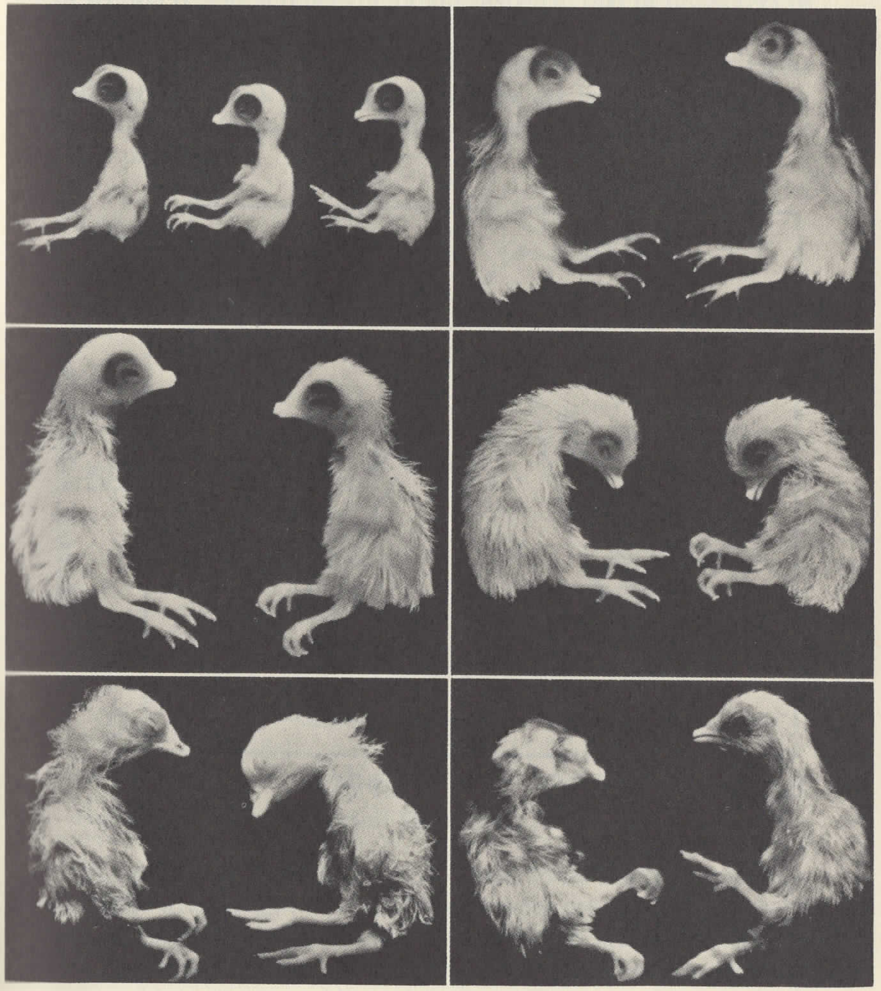

FIGURE 4. Embryonic stages of development of normal and crooked toed chicks (Hicks, 1953)

some detail—crooked toes in chickens and extra venation in *Drosophila*. A number of other cases will be referred to in less detail in section 9, and another important instance, that of podoptera in *Drosophila*, analysed in section 15.

Crooked toes in chickens have been described briefly by Hicks and Lerner (1949). The data cited here are largely based on the work of Hicks (1953), whose forthcoming publications will present other particulars.

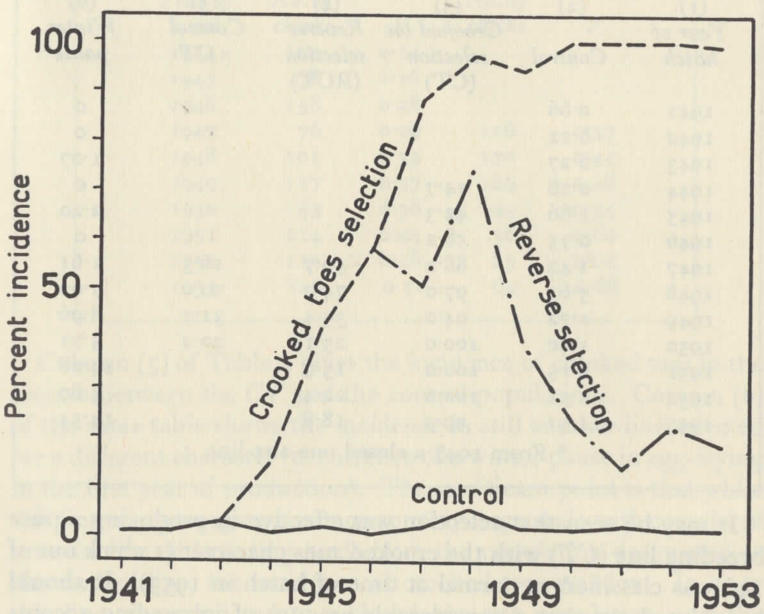

FIGURE 5. Selection experiment for increased incidence of crooked toes

In most closed populations of domestic fowls a small percentage of chicks with a slight flexing of one or more toes may be observed at hatching-time. Under selection both the incidence and the severity of the defect can be increased, the condition eventually approaching one resembling club feet. Figure 3 shows a chick with a reasonably severe expression of crooked toes, and Figure 4 illustrates normal and affected embryos in various stages of development. Figure 5 shows the course of a selection experiment for increased incidence of the defect, the details of which are given by the data in Table 4. The control line was one selected for egg production in which no individuals with crooked toes were used as parents. In later years selection against the defect was made more stringent, no individuals from families in which the defect was manifested being chosen as parents.

TABLE 4

Percentage incidence of crooked toes in chickens (Hicks, 1953 and unpublished)

(1) *Year of hatch*	(2) *Control*	(3) *Crooked toe selection* (CT)	(4) *Reverse selection* (RCT)	(5) *Control* × CT	(6) *Winter pause**
1941	0·66				0
1942	0·22				0
1943	2·27				1·07
1944	0·28	14·7			0
1945	1·86	42·3			2·20
1946	0·75	58·2			0
1947	1·42	88·2	50·7	16·5	1·61
1948	5·63	97·0	74·0	20·0	7·02
1949	1·72	94·0	39·4	31·7	8·96
1950	1·40	100·0	23·1	20·2	5·71
1951	2·15	100·0	13·9		14·28
1952	1·31	100·0	22·4		4·80
1953	1·31	99·3	18·8		14·54

* From 1947 a closed one-sire line

It may be seen that selection was effective in producing a pure breeding line (*CT*) with the crooked toes character (1 chick out of 146 was classified as normal at time of hatch in 1953). It should be pointed out that a considerable amount of inbreeding accompanied the selection, the inbreeding coefficient rising to about 40 per cent at the time the 100 per cent level of incidence was reached. Reverse selection (*RCT*) was started in 1947, but so far complete elimination of the defect in the back-selected line has not been attained (though the coefficient of inbreeding in this line reached 0·60 in 1951). At the beginning of selection for increased incidence of crooked toes, no marked decreases in fitness occurred. With an increasing amount of inbreeding the reproductive capacity of selected parents dropped somewhat, but with attainment of 100 per cent incidence it began to improve. At the present time no difficulties in reproducing the *CT* line are being experienced.

On the other hand, the fitness of the *RCT* line has continually dropped and only a few survivors are available each year for reproduction. Table 5 gives statistics regarding the number of chicks hatched and the inbreeding coefficients in the two lines.

TABLE 5

Inbreeding coefficients (*F*) of the CT and RCT lines

	CT *line*		RCT *line*	
Year of hatch	*No. of chicks*	*F*	*No. of chicks*	*F*
1944	102	0·14		
1945	78	0·26		
1946	158	0·28		
1947	76	0·29	116	0·37
1948	101	0·32	100	0·44
1949	117	0·37	109	0·48
1950	43	0·38	39	0·54
1951	114	0·44	36	0·60
1952	114	0·48	85	0·64
1953	146	0·51	64	0·68

Column (5) of Table 4 gives the incidence of crooked toes in the crosses between the *CT* and the control populations. Column (6) of the same table shows the incidence in still another line selected for a different character (occurrence of a winter pause in egg-laying in the first year of production). The significant point is that while this line was propagated on a reasonably large scale with occasional introduction of breeding birds from the population designated as the control line, the incidence of crooked toes was low. In 1947 this line was restricted to a closed one-sire population, and the incidence of crooked toes rose rapidly.

The correlation between the level of inbreeding and the incidence of crooked toes is demonstrated in Table 6, which shows the percentage of the defect in 8 other inbred lines extracted from the control population, lines in which no selection with respect to crooked toes was practised. While considerable variation is found between lines, the incidence in them eventually became in all cases higher than in the foundation stock. Crosses between these lines were made in various combinations in 1949, 1950 and 1951. The average unweighted percentage incidence of 18 crosses (in which every one of the lines was represented), was 1·1 per cent above

TABLE 6

Number of chicks (*N*), inbreeding coefficient (*F*) and percentage incidence of crooked toes (%) in inbred lines of chickens (Hicks, 1953; Schultz, 1952; and unpublished)

Line Numbers		*Years of hatch* 1945	1946	1947	1948	1949	1950	1951	1952	1953
1	*N*	158	138	133	81	117	29	25	21	19
	F	5	23	31	41	49	47	56	59	61
	%	0	0	3	27	5	28	16	10	16
2	*N*	205	81	153	82	135	53	16	10	1
	F	2	19	30	41	52	58	63	67	74
	%	0	3	4	13	6	8	13	20	100
3	*N*	125	165	121	47	111	105	63	40	95
	F	2	22	30	37	39	39	47	52	59
	%	0	1	1	21	5	2	2	3	21
4	*N*	67	74	58	65	91	95	56	51	45
	F	4	15	26	35	43	48	52	58	64
	%	0	0	2	12	13	11	11	4	4
5	*N*	137	170	79	122	76	39	49	29	112
	F	4	17	23	24	31	38	42	46	52
	%	2	0	3	5	7	5	2	6	5
6	*N*	122	89	38	51	46	42	19	50	22
	F	3	16	28	37	40	48	52	60	61
	%	0	3	13	18	0	21	5	10	27
7	*N*	141	82	76	60	64	57	22	65	65
	F	9	18	30	32	46	50	57	64	67
	%	0	1	0	30	13	16	14	32	60
8	*N*	150	166	172	63	50	7	7	8	29
	F	0	21	27	38	42	42	48	52	58
	%	0	0	0	2	2	0	0	25	17

TABLE 7

Percentage incidence of crooked toes in backcrosses of F_1 (CT × Control) males to the females of the parental lines (Hicks, 1953)

	Phenotype of male parent *Normal*	*Slight CT*	*Moderate CT*	*Severe CT*	Number of chicks
Female parent					
Control	5·4	16·7	16·7	16·7	108
Crooked toe	53·1	80·6	90·9	69·0	73
Number of chicks	69	54	16	41	180

that of the incidence of the lower parent in the year of the cross, and 4·1 per cent below that of the mid-parental value. Expressed in another way, in 5 cases the incidence in the cross was below that of the lower parent, in 5 cases it was equal to the lower parent (which in 3 of the 5 cases had zero incidence), and in 8 cases intermediate between the two parents.

Finally, Tables 7 and 8 give some results of backcrosses and F_1 *inter se* matings, in relation to the phenotypes of the birds entering the cross. Without detailed discussion of the figures reported in these tables, it may be clearly seen that at best a number of supplementary assumptions regarding penetrance and expressivity are necessary to fit the results to a relatively simple Mendelian scheme.

TABLE 8

Percentage incidence of crooked toes in the F_2 (CT × Control)
The figures in parentheses give the number of chicks
(Hicks, 1953)

Paternal line	*Maternal line*	F_1	*Phenotypes of F_1 parents mated* *Normal × Normal*	*Normal × CT*	*CT × CT*
97·0	5·63	11·7	44·7 (38)	32·7 (52)	63·2 (19)
5·63	97·0	28·2	7·4 (108)	10·7 (75)	— —

All in all, on the basis of the data cited here and of other material reported by Hicks (e.g. a survey of incidence in a number of U.S. flocks of chickens of various breeds and in various locations), we can summarize the behaviour of the crooked-toes character by listing the following points:

1. The hereditary elements for crooked toes are probably present in all stocks of chickens.
2. A sporadic incidence at a very low rate can be observed in a great majority of flocks, phenotypic selection against the character being ineffective.
3. The incidence of crooked toes increases under inbreeding with or without selection.
4. Inbreeding combined with selection can lead to fixation of the trait.

5. Expansion in size of the population breeding pure for the character, and thus a reduction in rate of inbreeding, permits at least a partial restoration of reproductive fitness.
6. Successful reverse selection with inbreeding is relatively more difficult than the original selection for crooked toes.
7. The behaviour of crosses between lines with various degrees of incidence of the defect is unpredictable.
8. In general, outcrossing tends to lower the level of incidence.
9. Expressivity increases with incidence even when selection is directed only towards higher incidence and not towards the degree of manifestation, or in cases of inbreeding where no selection is practised.

These conclusions are not at variance with an interpretation of the inheritance of crooked toes on the basis of a relatively large number of multiple recessive genes with variable penetrance. At the same time the similarity between the behaviour of this trait and the characteristic features of inbreeding degeneration is striking and is accentuated by the ubiquity of the genes responsible for the character in flocks of various breeds. The question regarding the nature of the mechanism by which these genes are maintained in all populations naturally arises. Considerable light on this problem is shed by the work of Dubinin (1948) on another phenodeviant, extra veinlets in *Drosophila.*

8. WING VENATION IN *DROSOPHILA*

In a survey of a large number of wild populations of *D. melanogaster* which included over 140,000 flies, Dubinin found an average incidence of 0·29 per cent of several types of extra wing veinlets. A seasonal cycle of variation was noted with an increase in occurrence at the time of the most rapid multiplication of population size.

Selection and inbreeding were capable of modifying incidence and expression. In particular, while in natural populations two types of extra wing ('free veinlet' and 'veinlet 2') appeared together in the same fly 1/24th as often as they did separately, most of the inbred selected lines had both manifestations together. A graded series of increasing expression of these types culminated in the extreme character designated 'network', and some of the inbred lines attained a 100 per cent incidence of this type. Other inbred lines stabilized at various levels of occurrence and expression. The incidence in crosses between them was unpredictable, the results varying from complete recessivity to semi-dominance.

One of the most significant experiments conducted by Dubinin in this study consisted of the propagation by brother × sister matings of the offspring of normal pre-fertilized females captured in nature. Out of 240 lines established in this manner from one population, 163 (67·9 per cent) showed extra veins within 30 generations of inbreeding. Lines from 5 other populations from diverse locations varying in ecological properties showed a similar appearance of the defect within 15 generations of inbreeding in 76·2 per cent of 147 cases. The distribution of the first appearance of phenodeviants according to the generation of inbreeding suggests that it is not unlikely that a greater percentage of, if not all, the lines from the wild females were contaminated with genes for the character. In one instance the first fly with extra veinlets appeared in the 22nd generation of brother × sister mating. The extreme form of the expression, network, did not make its first appearance in one case until as late as the 9th generation.

Studies on other species of *Drosophila* suggested a similar prevalence of concealed extra-venation genes. Inbred matings of the same type as in *D. melanogaster* were made in *D. transversa*, *D. falerata* and *D. obscura*, with 20–30 per cent of lines showing extra veins in the first generation (figures comparable to that for *D. melanogaster*).

A chromosome analysis in the latter species demonstrated that polygenes responsible for the production of the phenodeviant were concentrated in the second chromosome with two primary centres of activity at the loci *net* (0·0) and *blistered* (107·3).

The maintenance in the populations studied of the hereditary elements producing extra veins in a multiple recessive state was interpreted by Dubinin on the basis of a selective advantage of heterozygotes. In support of this viewpoint he presented data comparing the viability of heterozygotes carrying elements of the extra venation complex with that of individuals free from them. A Curly stock with inversions was crossed with a control stock (free from extra venation and designated as *N*), and with three different extra veinlet stocks (designated as *E*). The offspring from these crosses were then mated to *NN'* flies in the first case (*N'* standing for a wild chromosome also free from the extra veinlet complex) and with *NN* flies in the second case. The distribution of the types of progeny obtained was:

	CyN × N′N	*CyE × NN*
CyN	51·9%	47·9%
NN′	48·1%	—
EN	—	52·1%

The difference between the two cases, based on some 40,000 flies in the experiment, was significant, demonstrating the higher viability of the extra veinlet heterozygotes.

The particular points that may be emphasized with respect to the genetic behaviour of extra veinlets are:

1. the ubiquity of the genetic potential for the expression of the character not only in individuals of one population but in different populations and various species of the genus *Drosophila*;
2. the heterogeneity of the polygenic system for extra veinlets, involving variability in incidence and expression, and non-allelism in different lines;
3. the control of the system by segregating and recombining polygenic blocks organized within the second chromosome.

It should be pointed out that an alternative interpretation of Dubinin's material on the basis of a number of specific pleiotropically acting major mutants has been advanced by Goldschmidt (1953), who considers that Dubinin has failed to recognize the mutants *blistered* and *net* (see Goldschmidt, 1945) segregating in his population, and that the rest of his interpretation is gratuitous.

No comment can be made here on the validity of the original observations. It seems, however, that even if Goldschmidt's statement is accepted, that Dubinin's material consisted of carriers of definite mutations previously described and located, Dubinin's basic interpretation is not invalidated. Goldschmidt does not deny the existence of penetrance and dominance modifiers, so that the major effect of accepting his explanation of Dubinin's results is to shift the polygenic system from the mutants directly affecting venation to their modifiers. The ubiquity of these genic elements has still to be accounted for in Dubinin's terms. Furthermore, the history of the first appearance of all three major forms of expression (free veinlet, veinlet 2, and network) in the inbred offspring of the pre-fertilized wild females is hardly susceptible to an explanation in terms of single mutant genes floating in the population.

For the milder form of expression, on the assumption most favourable to Goldschmidt's thesis, each wild female or her mate would have transmitted one chromosome carrying an extra venation mutant to the first laboratory generation of any line which eventually exhibited the phenotypic deviation. The probability of two + + flies being selected as the parents of the next generation would be 1/4 (unless the heterozygote did indeed have a higher viability, as claimed by Dubinin). That for selecting two heterozygotes would similarly be 1/4. In the first case, no matter how much inbreeding were used later, no extra veins would appear. In the second case, extra veins would be produced in the following generation. The probability of the trait remaining cryptic is reduced by one-half in every succeeding generation, so that by the 10th generation it is 1/512. Yet 5·6 per cent of the lines eventually showing the trait did so only after 11 or more generations of brother × sister mating. The discrepancy is, of course, greatly increased if more than one carrier chromosome entered the first cross, whether the 'contamination' was at one or at several loci.

For network, whose appearance is attributed by Goldschmidt to the gene ***net*** with 100 per cent penetrance and expressivity, the expected distribution of first appearance is contrasted below with the observed, once more assuming a situation most favourable to Goldschmidt's thesis, i.e. that no other mutants are involved in these lines (should there be some, network would have appeared even earlier):

Generation of first appearance	*Expected number of lines*	*Observed number of lines*
2	11·5	3
3	5·8	6
4	2·9	5
5	1·4	4
6	0·7	3
7	0·4	0
8	0·2	1
9	0·1	1

The discrepancy between expectation and the observed number (pooling the 3rd and subsequent generations and applying a correction for continuity) is significant.

We shall return later to Dubinin's detailed interpretation and consider concurrently with it another important phenodeviant, podoptera, in *Drosophila*. This character is the one for which the most complete genetic analysis is available. The details are given in the monograph by Goldschmidt, Hannah and Piternick (1951) but our discussion of this case will fit better into the more theoretical section 15.

9. OTHER PHENODEVIANTS

Next to podoptera the most elaborately analysed instance of phenotypic deviants in *Drosophila melanogaster* is that of abnormal abdomen (*AA*). It was studied in a Dichaete strain established by Sobels (1952) from a laboratory stock in which asymmetric abnormalities of the head, thorax and abdomen were manifested in the pupal stage. The findings of Sobels relative to the points under discussion may be summarized as follows:

1. The basis of *AA* is a balanced polygenic system involving several of the chromosomes.
2. Selection for higher incidence was possible from a level of 4·4 per cent to 28–31 per cent, beyond which it had no further effect. Reversed selection at this point was ineffective.
3. Temperature and time of hatching had an effect on incidence.
4. Irregular dominance in crosses with other stocks is found in the presence of Dichaete.
5. Another Dichaete stock showed tergite abnormalities and was successfully selected to a level of incidence of 39 per cent. Although this character was somewhat different from the first one in expression, the two selected stocks exhibited similar genetic behaviour.
6. Selection was not based entirely on offspring from brother × sister matings. It is difficult to evaluate how much inbreeding was practised, but it is obvious that some was.

Sobels concluded that '*AA* genes apparently are present as balanced polygenic combinations in various strains. The presence of Dichaete exerts an intensifying influence on the manifestations of these genes. Then selection may be effective till a state of homozygosity of the different factors had been attained.'

The similarity between these features and those of the phenodeviants previously discussed is obvious and requires no further comment. Whether other instances that may be cited for *Drosophila* parallel as closely the situation described for extra vainlets and the one to be described for podoptera cannot be said with any degree of assurance. There are no doubt differences in the exact genetic behaviour of different phenodeviants, but it is their more general aspects that we wish to emphasize here. On this premise it is not an unreasonable speculation that at least some of the so-called homoeotic mutants studied by Goldschmidt and his students (e.g. Villee, 1942), a number of Russian workers (e.g. Astauroff, 1929; Balkashina, 1929) and others, belong to the class of phenodeviants. The same may be said for the benign melanotic tumours investigated by Barigozzi (1952) in *D. melanogaster*, and found in a variety of other species by Brncić and Koref (1952) and by Milani (1952), and for wing venation abnormalities in *D. subobscura* studied by Prevosti (1952).

Though in some of the above instances specific genes were presumed to have been isolated, precise identification of the loci involved may not have been achieved because of the variable penetrance and modifiability of these characters by the genetic background. Indeed it was Goldschmidt (1938) himself who suggested, in view of the concentration of many homoeotic mutants in the right arm of the third chromosome, that whole chromosomes rather than individual genes are the units of heredity.

There are many traits in higher animals which demonstrate a pattern of inheritance resembling the cases described. One of the most extensively studied instances in mammals is otocephaly in the guinea pig (Wright, 1934*a*). This is a monstrosity expressed in its lowest form as a jaw defect, and in its highest as a virtual absence of the head. The character is very rare in most strains (less than 0·05 per cent incidence), but one strain produced by inbreeding had a level of occurrence of 5 per cent. A number of sub-branches of this strain have been propagated, the frequency in all but one being approximately the same, the exception having an incidence of 27 per cent with a tendency to relapse to the lower value. The increase from 5 to 27 per cent was found to be due to a dominant mutation segregating as a unit.

The genetic explanation supplied by Wright is that the strain 'must be considered as homozygous for a certain gene complex. It is shown that within this strain the monsters cannot be due to ordinary Mendelian segregation and that there are no balanced lethal factors. Neither can the monsters be due to any important extent to environmental factors of such a sort as to act on litter-mates alike. The randomness of occurrence within litters of each size indicates that each monster is due to a highly localized chance event, supplementing a genetic tendency common to all members of the group. . . . The genetic complex determined merely the percentage incidence in a strain, while chance differences of such a nature as to be practically as great between litter-mates as between non-litter-mates of the same genetic constitution, are decisive with respect to individuals.'

It should be noted that the chance differences referred to are not necessarily only of environmental origin, but could equally well have a Mendelian basis, in the sense that varying levels of degrees of homozygosity for many loci would be arrived at by chance.

Another mammalian case is polydactyly in mice, which occurs in many strains and inbred lines. Holt (1945) summarized the studies of eight different investigators on polydactyly occurring as a 'separate inherited entity' and in association with other defects, while Chase (1951) added another instance. The latter also noted the sporadic incidence of the trait in his laboratory in a number of inbred strains unrelated to the stock in which he studied the effect thoroughly.

In no case is clear-cut Mendelian inheritance apparent, and although Holt postulated a single recessive gene with incomplete penetrance, it seems doubtful, as noted by Chase, that this is an adequate explanation of the situation.* All the data presented by the various investigators seem to point to the following properties of the character:

1. low sporadic incidence in many stocks;
2. increase in incidence under continued inbreeding with selection;
3. failure of appearance of the trait in first crosses between polydactyls of different origin (see Holt and Wright, 1946, in addition to the works already cited).

Other traits with more or less similar genetic characteristics (though it must be stressed that only fragmentary evidence is available for some of these) include polydactyly in guinea pigs (Wright, 1934*b* and *c*), pedal anomalies in mice (Kobozieff and Pomriaskinsky-Kobozieff, 1950), a whole series of characters in rodents (dental abnormalities in mice and homoeotic variations in rabbits) listed with literature references by Grüneberg (1952), and the kinky-tail trait in pigs (Donald, 1949).

Many other abnormalities have been described in various species. It is rather problematic whether a high proportion of them can be placed in the category of phenodeviants, at least if this term is reserved for traits inherited on the basis of point 5 listed in section 2 of the present work. Nevertheless, it may be worth while to examine from this viewpoint such diverse traits as the irregularly inherited abnormalities of the abdomen in *Drosophila* listed in the literature review by Sobels (1952), the morphological defects in mice enumerated by Eaton (1952), and the numerous puzzling characters in plants (which in the case of self-fertilized species may depend on the converse of the process postulated for Mendelian populations, i.e. segregation of heterozygotes), such as rogues in tomatoes (Crane, 1948) and in peas (Bateson and Pellew, 1920; Renard, 1930).

10. VARIABILITY OF HETEROZYGOTES

It has been recognized by many investigators that one of the features of inbreeding depression may be an increased variability of environmental origin. One interpretation that has been advanced for this observation (for instance, by Rasmusson, 1949) is that, while genetic variance decreases as higher levels of homozygosity are reached, the generally reduced vitality of inbred individuals makes them more susceptible to uncontrolled fluctuations in their environment, and thus produces a greater range of phenotypic expression of their metric traits. Under this interpretation it is the lower adaptedness of highly homozygous individuals that leads to an increase in environmental variance.

The alternative explanation proposed here is that loss of heterozygosity tends to reduce the buffering properties of individuals from normally highly heterozygous populations (i.e. to increase their lability), so that low viability and increased variance are not cause and effect, but concomitant consequences of inbreeding. This idea was expressed in a more general way by Donald (1948), who suggested that departures from the breeding system normal for the species (i.e. either inbreeding or excessive outbreeding)

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* See, however, Fisher (1953) for additional evidence for a single gene basis of Holt's case.

'will reduce the stability of a particular developmental process to the point where it can be easily upset by genes previously incapable of upsetting it, or by some accident of environment during the susceptible stage'.

It is not possible at the present stage of our knowledge to discriminate between these two interpretations, but we can consider what evidence there is for the notion underlying both alternatives, i.e. that the environmental variability of a Mendelian population is a function of its relative heterozygosity. At this point we have to depart somewhat from our plan of presenting the data first and the discussion later. This procedure is dictated by the necessity for clarifying the particular type of evidence sought. Hence, some largely theoretical points are considered in this section, the data are reviewed in sections 11 and 12, and further discussion is undertaken, beginning with section 13.

There are several problems connected with an attempt to verify the general idea that heterozygotes are better canalized than homozygotes. The ideal test would consist of comparisons of environmental variability in fitness of these types. Unfortunately, practically no data are available on this point. As a consequence, the survey of buffering capacity of heterozygotes and homozygotes must be based on individual phenotypic characters rather than on fitness. There are several different ways in which this property can express itself. Firstly, it is possible that under relatively stable conditions of environment normal for a particular organism, the range of variability of some traits will be less in a group of heterozygotes than in a homozygous population. Secondly, when shifts in the conditions of existence occur, either because of a change in the external environment or because of the appearance of a mutant, the extent of phenotypic difference from the original form may be less in heterozygotes than in homozygotes. Thirdly, the variation in the expression of bilateral or serially arranged characters may be found to be less in individual heterozygotes than in individual homozygotes. Fourthly, repeatable reactions to some stimulus may have less amplitude of expression in heterozygotes than in homozygotes.

There is little or no directly collected evidence on most of these points, and the information available is, as a rule, a by-product of investigations conducted for other purposes. It will probably be simplest to review the various data from the literature on these points, with particular reference to the first one, since the bulk of the available information refers to it (see, however, the exchange of opinion between Heuts and Brieger, in Brieger, 1949). But the first task is to specify more precisely the basis of the hypothesis.

It may be recalled that Gustafsson (1946) proposed a generalization exactly contrary to the one suggested here, i.e. that the phenotypic variability of single-gene heterozygotes is greater than that of homozygotes. He illustrated this proposition by material from his own investigations, and from earlier studies of Robertson on barley. However, this evidence comes from a naturally self-fertilized species in which it may be expected that the situation will be reversed from that postulated by us for cross-fertilized organisms.

Homozygosity is enforced under self-fertilization except in the case of balanced systems. Hence self-fertilized plants must have evolved in the direction in which homozygosity is not only tolerated but actually leads to greater adaptation. The difference between the two cases is well illustrated by the contrast in behaviour under inbreeding in chickens on the one hand, and barley on the other. In the former, Düzgüneş (1950), as already noted, found that natural selection favoured the more heterozygous individuals (as has Tantawy, 1952, for *Drosophila*). In the latter, Bateman and Mather (1951) found the opposite tendency. Incidentally, in their material there also seems to be some indication (though not a certain one, due to changes made in planting technique in the course of their experiments) that environmental variance was reduced by inbreeding, in accordance with Gustafsson's postulate.

Gustafsson himself did not examine the situation in cross-fertilized plants. He cited only the results of average computations based on Mangelsdorf's (1928) mutant in maize and on Karper's (1930) mutant kafir, as, in a general way, bearing out his conclusions with barley. If we examine the data from these two sources in the identical manner in which Gustafsson treated the barley material, the picture emerging fails to substantiate this assertion. Table 9 presents the ratios of the coefficients of variation of the heterozygotes to those of the homozygotes for the data on different traits which the two investigators made available in their papers. Whereas in barley the majority of such ratios were above one, indicating the greater variability of the heterozygote, in maize and kafir no such preponderance can be observed.

Thus, while it cannot be said that Mangelsdorf's or Karper's data lend any particular support to the hypothesis developed here, it is also true that they do not bear out Gustafsson's generalization.

Alternative models of individual development, one of which leads to Gustafsson's hypothesis (if we extend it to multiple heterozygotes) and the other to the one suggested here, may be represented schematically as in figure 6. In each case the point of departure is a zygote of a given genetic constitution, largely homozygous for the inbreds, largely heterozygous for crosses between inbred individuals. In both instances populations of such zygotes are genetically homogeneous. The curves originating from each zygote represent courses of development of individuals, the variation between them being naturally of environmental nature.

TABLE 9

Ratio of the coefficients of variation of the heterozygous to that of the homozygous plants (data on maize from Mangelsdorf, 1928; on kafir from Karper, 1930)

Plant	*Character*	*Ratio*
Maize	Height at 33 days	1·10
	„ „ 43 „	1·06
	„ „ 53 „	0·95
	„ „ 63 „	0·92
	„ „ 73 „	0·90
	„ „ 83 „	0·89
	Days to anthesis	1·00
	Length of ears	0·96
	Weight of ears	0·87
Kafir	Height at 20 days	1·27
	„ „ 40 „	1·02
	„ „ 60 „	0·98
	„ „ 80 „	0·91
	„ „ 137 „	0·73
	Plant weight at maturity	0·87
	Weight of heads	0·94
	Length of heads	1·14
	Days to full boot	1·05
	Days to first bloom	1·06

The left side of the figure shows a model based on the viewpoint that phenotypic variance is smaller in homozygotes than in heterozygotes. The heavy vertical lines enclosing the unshaded area represent the range of adaptation of the homozygous population of zygotes. Should environmental stresses carry the course of development of a homozygote into the shaded area, the individual does not survive. Heterozygotes, having on the other hand a wider range of tolerance of unfavourable environmental conditions, can follow curves within the unshaded area. Hence at the point in the course of development where the phenotypic expression of a trait is measured (where the dashed lines begin), the variability of the hybrids will be greater than that of the inbreds.

The right part of the figure illustrates the alternative model. The heavy perpendicular lines here not only serve to demarcate the ranges of phenotypic expression of homozygotes and heterozygotes, but also indicate the channels within which the development of the individual is directed by its genotype. The heterozygotes, having better buffering capacities than the homozygotes, do not allow environmental (or residual genetic) forces to take individual curves of development outside the unshaded inner channel. The homozygotes, not being as strongly canalized, have a broader range of phenotypic expression. It might be reasonable to assume that homozygotes of alternative allelic constitutions would have extended their channels either to the left or to the right of the heterozygote channel, but not necessarily in both directions. Be this as it may, the phenotypic variance of the inbreds will, in this model, be greater than that of the hybrids.

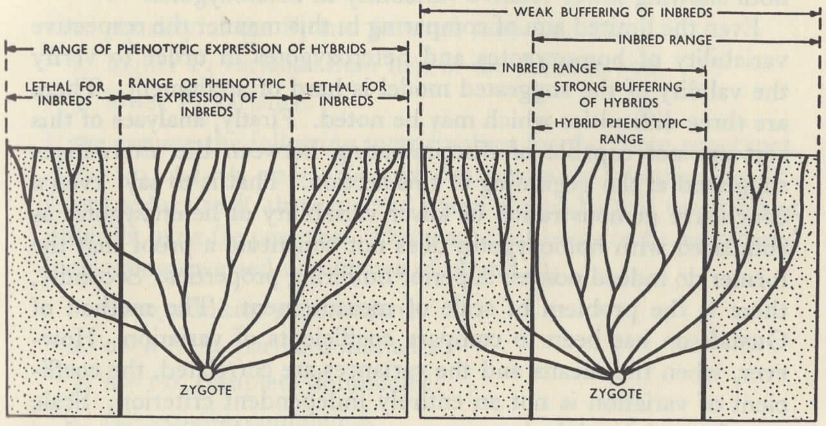
RANGE OF PHENOTYPIC EXPRESSION OF HYBRIDS
LETHAL FOR INBREDS
RANGE OF PHENOTYPIC EXPRESSION OF INBREDS
LETHAL FOR INBREDS
ZYGOTE
WEAK BUFFERING OF INBREDS
INBRED RANGE
INBRED RANGE
STRONG BUFFERING OF HYBRIDS
HYBRID PHENOTYPIC RANGE
ZYGOTE

FIGURE 6. Models of developmental buffering (see text)

The basic test of the hypothesis advanced should be whether the environmental variance of heterozygotes is greater or smaller than that of homozygotes, particularly with respect to the traits of adaptive significance. Since it is not always possible to decide what trait is directly adaptive, perhaps a better criterion is to consider characters which exhibit heterosis. While it is not sound to identify adaptive value with heterosis in all cases, we may nevertheless pay particular attention to heterotic traits. It may be noted in passing that in Table 9 no such traits are included in Mangelsdorf's material, while in Karper's data the clearly significantly heterotic traits are height at 137 days and plant weight at maturity, both showing lower relative variability in heterozygotes.

Even the limited aim of comparing in this manner the respective variability of homozygotes and heterozygotes in order to verify the validity of the suggested model is hard of attainment. There are three difficulties which may be noted. Firstly, analyses of this sort are not capable of discriminating between the alternatives suggested at the beginning of this section. That is to say, even a conclusive demonstration of lower variability of heterozygotes as compared with homozygotes does not constitute a proof that the former do indeed possess superior buffering properties. Secondly, there is the problem of scale of measurement. The method of Gustafsson has been to compare coëfficients of variation. However, when the means and the variances are correlated, the coefficient of variation is not an entirely independent criterion. Scale transformation might be necessary to remove this limitation, but the actual scale of measurement on which natural selection operates to reduce variability in adapted populations cannot be known. There is hence considerable uncertainty as to the exact interpretation of any measure of variability. This must be kept in mind when weighing the data from the literature which are presented below.

The third problem lies in the fact that variances of inbred lines and of crosses between them are usually reported in phenotypic terms. Thus they represent sums of the genetic and environmental components, possibly with interaction terms added. Under inbreeding the genetic component of variance may be generally expected to decrease as high levels of homozygosity are attained, though at first it may rise as initially rare recessive genes increase in frequency (A. Robertson, 1952). On the other hand, on the present hypothesis, the loss of buffering properties under inbreeding will tend to increase the environmental component. The net effect on the phenotypic variation of inbreds will then depend on the balance between these opposing tendencies. To clarify this matter we may consider briefly the expected variability of genetic origin in crosses between inbred lines.

When a cross is made between inbred lines the genetic variance of the F_1 will be zero only if there is complete homozygosis of each of the parents. In other cases the expectation varies with the gene frequencies and the degree of dominance. We may examine this question (discussed for the F_2 by Muller, 1936) somewhat more closely to show that three possibilities exist, i.e.:

1. equality of the F_1 and parental variance;
2. higher F_1 variance than that of the parents, and
3. lower F_1 variance.

If we assume the following metric values for the three genotypes, $AA = 1\cdot 0$, $Aa = h$, $aa = -1\cdot 0$, we can compute, by assigning different values to h, the expected parental and hybrid variances at different gene frequencies. There are four cases to be considered (neglecting reversed dominance of A and a):

1. $h = 0$, additive gene action;
2. $0 < h < 1\cdot 0$, partial dominance;
3. $h = 1\cdot 0$, complete dominance;
4. $h > 1\cdot 0$, overdominance.

Taking q as the frequency of allele A, with subscripts 1 and 2 to designate the two parental populations, we can see that in general, the parental mean will be

$$M = q^2 + 2q(1-q)h - (1-q)^2,$$

with a genetic variance

$$\sigma^2 = q^2 + 2q(1-q)h^2 + (1-q)^2 - M^2.$$

The mean of the F_1 will similarly be

$$M = q_1q_2 + (q_1 - 2q_1q_2 + q_2)h - (1-q_1)(1-q_2),$$

with a genetic variance,

$$\sigma^2 = q_1q_2 + (q_1 - 2q_1q_2 + q_2)h^2 + (1-q_1)(1-q_2) - M^2.$$

Substitution into these expressions of various values of q and h leads to several generalizations:

1. Under additive gene action the mean and the variance of the F_1 are equal to the respective averages between the parents, whatever the gene frequencies.
2. In other cases, the mean and variance of the F_1 are equal to those of the parents when $q_1 = q_2$.
3. Otherwise, the mean of the F_1 is always higher than the average of the parental means.
4. The variance of the F_1 under partial dominance, complete dominance and overdominance is higher than the average of the parental variances when q_A in the F_1 is less than 0·5; it is lower than the average of the parents when q_A in the F_1 is greater than 0·5; and when q_A in the F_1 is equal to 0·5 the F_1 variance is equal to the average variance of the parents.

TABLE 10

Means and variances of crosses between lines differing in q_A

The genotypic values are assumed to be:

$AA = 1{\cdot}0$; $Aa = 1{\cdot}5$; $aa = -1{\cdot}00$.

		Means		*Variances*	
q_{A1}	q_{A2}	*Average of parents*	F_1	*Average of parents*	F_1
0	0	−1·000	−1·00	0	0
	0·1	−0·765	−0·75	0·4721	0·5625
	0·5	−0·125	0·25	0·5313	1·5625
	0·9	0·035	1·25	0·0401	0·5625
	1·0	0	1·50	0	0
0·1	0·1	−0·530	−0·53	0·9441	0·9441
	0·5	0·110	0·35	1·0033	1·5025
	0·9	0·270	1·23	0·5121	0·5121
	1·0	0·235	1·45	0·4721	0·0225
0·5	0·5	0·750	0·75	1·0625	1·0625
	0·9	0·910	1·15	0·5713	0·3025
	1·0	0·875	1·25	0·5313	0·0625
0·9	0·9	1·070	1·07	0·0801	0·0801
	1·0	1·035	1·05	0·0401	0·0225
1·0	1·0	1·000	1·00	0	0

As a more specific illustration we may inspect an example of overdominance to see the relationship between the F_1 variance and heterosis. Table 10 shows the means and the variances when $h = 1{\cdot}5$.

It may be seen that heterosis in this example is obtained when q is high in at least one of the parents. Both increases and decreases in the variances of the F_1 may be noted. In general, the F_1 variance tends to be lower than the average inbred parental variance when the parents are still somewhat heterozygous and the F_1 is heterotic. This follows from the fact that since q_A in one parent must be high to produce F_1 heterosis, the q_A of the F_1 will be over 0·5 if the other parent still carries the A allele. There are, however, situations in which, depending on q and h, the genetic variance of the heterotic F_1 is equal to or greater than the average of parental variances.

There is no *a priori* way of deciding what the environmental variance of the F_1 compared to that of the parents will be. On the hypothesis of developmental homeostasis here presented it may be expected to be smaller. Examination of the phenotypic variances of the F_1 between inbred lines can thus at best give us only a clue as to whether this notion is likely to be correct, since even when the phenotypic F_1 variance is lower than the parental average, the reduction may have been due to the genetic and not to the environmental component. Only in instances of complete fixation of alleles can unequivocal evidence be had. This obviously demands specific experimental designs, such as those in the work of Dobzhansky and Wallace (1953). Their experiments were arranged to test the abilities of heterozygotes and homozygotes to maintain variability in survival value within the range of sampling error, when subjected to differences in environment such as prevail in replicate cultures. The results showed that heterozygous combinations in *D. pseudoobscura*, *D. persimilis*, *D. prosaltans* and *D. melanogaster* had uniform survival rates, while homozygous combinations exhibited significant heterogeneity between cultures. The authors' conclusion is that 'homeostatic adjustments are superior in heterozygotes to those in homozygotes'. Their data provide the strongest link in the chain of evidence we have on the rôle of heterozygosity in developmental homeostasis. Other available literature is subject to the various limitations noted. The evidence is widely scattered and it does not seem profitable to examine in detail every instance that has a bearing on the problem. A few typical examples in a variety of forms may, however, be considered and reference made in passing to a number of others which support or contradict the thesis advanced.

11. VARIANCE OF HETEROZYGOTES IN *DROSOPHILA*

A suggestion that heterozygosity is responsible for uniformity of fitness components in *Drosophila* is provided by the fact that in crosses between inbred lines, lifetime egg production exhibits heterosis, although the range of the individual F_1 values does not transcend that of the parents (Gowen, 1952). More precise indications are available from the study of Gowen and Johnson (1946). Table 11 shows the relative variability for several traits of two inbred races and the hybrid between them studied by these authors. With respect to duration of egg-laying and to survival, the hybrids do not differ notably from the inbred strains. So far as lifetime egg-production is concerned, the variability of the hybrid is strikingly less than that of the parental races. It may also be noted that this is the trait for which the hybrid is markedly superior to the inbred strains.

TABLE 11

Characteristics of two inbred races of *D. melanogaster* and of the hybrid between them (Gowen and Johnson, 1946)

Trait	*Race Ames I* (16 *generations of sib matings*)			*Race Inbred* 92 (92 *generations of sib matings*)			*Hybrid*		
	Mean	σ	*C.V.*	*Mean*	σ	*C.V.*	*Mean*	σ	*C.V.*
Lifetime egg production	1000	464·7	46	389	192·8	50	2034	633·6	31
Days in lay	38·4	13·25	35	17·2	8·14	47	43·4	16·89	39
Survival of females	50·9	14·86	29	33·4	11·14	33	50·0	17·83	36
Survival of males	49·6	18·20	37	44·0	18·43	42	55·4	20·02	36

Other data from the same source provide us with a rather strong confirmation of the hypothesis advanced. Gowen and Johnson found significant correlations (ranging from 0·65 to 0·90) between the means and the standard deviations of various characters in the different races compared. Now, the differences between the means of races reflect not only differences in the gene contents of the chromosomes they carry, but also their relative degrees of heterozygosity. This is obvious from the comparison of the descriptions of the races with their mean values, and may be seen from the following tabulation, showing the lifetime number of eggs produced by the different races, classified roughly on the basis of relative heterozygosity:

Most homozygous	*Relatively homozygous*	*Relatively heterozygous*	*Most heterozygous*
Inbred 92 = 389	Ames 1 = 1000	Ames 11 – 1511 = 1701	Hybrid = 2034
Homozygous 42 = 263	Florida 45 = 610		
Oregon R-C-44 = 413	Princeton = 814		
Swede C-40 = 390			

The regression of the racial standard deviation on the racial mean was found to be:

$$\text{S.D.} = 163 + 0{\cdot}28 \text{ Mean},$$

so that, as computed by the authors, a race averaging 300 eggs would have a standard deviation of 247, while one with a 2000-egg average would have a σ of 719. The respective coefficients of variation of these two races are then 82 and 36, indicating a considerable increase in variability with increasing homozygosity.

TABLE 12

Mean squares for bristle counts within cultures of inbred lines of *D. melanogaster* (Ramuson, 1951). Further explanation in text.

Inbred generations	*Abdominal bristles* ♂	♀	*Sternopleural bristles* ♂	♀
2–5 . . .	0·1416	0·1563	0·1387	0·1947
6–10 . .	0·1213	0·1317	0·1080	0·1325
11–15 . .	0·1281	0·1136	0·1087	0·1323
16–20 . .	0·1077	0·1173	0·0951	0·1356
60–70 . .	0·1576	0·1357	0·1005	0·1211
60–70 (*b* line excluded)	0·0897	0·0871	—	—
F_1 . . .	0·0818	0·0897	0·0904	0·1179
Four wild populations	0·1102	0·1203	0·1559	0·1913

Another example may be drawn from the inbreeding studies conducted by Rasmuson (1949, 1951). She considered the variability of abdominal and sternopleural bristles in a series of lines propagated by brother × sister matings. Bristle counts were converted to logarithms, making, variances independent of means. Mean squares within cultures for the different inbred generations, with degrees of freedom varying from 730 to 1350 for each value reported, are given in Table 12. The *b* line, excluded in the second figure given for the data of the 60–70 generations, is one in which variance of abdominal bristles increased under inbreeding. Clearly the F_1 has the lowest variance of sternopleurals and of abdominals when the abnormally behaving *b* line is not taken into account.

Selection tests performed on this line suggest that the residual variance of the sternopleurals after inbreeding is largely environmental (i.e. the component of specific interest to us), while that of the abdominals is connected with a balanced genetic mechanism.

A later report by Rasmuson (1952) illustrates another point in the problem under consideration. Studying the trend of variability she found that at first it increased within inbred lines. After some ten generations a stable level was reached somewhat below that of the original strains, with the F_1s between lines having a lower variance than the inbreds themselves or the original strains:

Ratio of intra-culture variance (*log transformation*)

Bristles . .	Abdominal		Sternopleural	
Sex . . .	♂	♀	♂	♀
Original strain / F_1	1·33	1·33	1·64	1·76
Inbred generation with lowest variance / F_1	1·25	1·30	1·04	1·07

In other words, a point of equilibrium between genetic and environmental variances appears to have been reached under inbreeding. It should be pointed out that Rasmuson recognized (as did, among other workers, Gordon in Anon, 1950, and, at least inferentially, Borissenko, Altshuler and Poliakov, 1935) that environmental variance depends on genetic constitution. More precisely, she attributed differences in this type of variance to polygenic balance, so that 'the poorer the balance, the more easily are the individuals influenced by environmental factors and the greater the phenotypic variation'. Furthermore, she suggested the identification of good balance with heterozygosity.

In a similar way, Robertson and Reeve (1952*a*), who found that the variance of wing length of the F_1 between inbred lines of *D. melanogaster* was reduced to 1·24 from the parental average of 2·35, specifically attributed the reduction to the greater biochemical versatility of heterozygotes as compared to the inbreds.* This suggestion was also made earlier by Everett (1950) in connexion with his study of suppressor genes in corn.

Further evidence on the variability of sternopleural bristles is provided by the study of Wigan (1944). For an unidentified reason his data for males had a large error. The variability of heterozygotes was greater than that of the homozygotes in this sex, but

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* I am informed by Professor J. B. S. Haldane that in his forthcoming book on biochemical genetics this viewpoint is discussed in some detail.

the error terms (or chromosome interactions) make interpretation difficult. In the females the results were clear-cut. Families were established in which homologous wild chromosomes came from the same individual (inbred), and others in which they came from different individuals from the same location (outbred). The comparison of mean squares for the two groups of families is as follows:

Chromosomes	I	II	III
15 outbred families . . .	0·3045	0·1492	0·3566
9 inbred families . . .	0·6010	0·5122	0·8499

However, when wild homologues originating from different localities were paired, the variance was increased over the outbreds, though it was still not as high as in the inbreds:

Chromosomes	I	II	III
3 inbred families . . .	1·1953	2·3805	0·8082
4 outbred (different location) .	0·5659	0·0487	0·2826
2 outbred (same location) .	0·2965	0·0421	0·0288

Wigan has interpreted these results as indicating that a balance between too much and too little inbreeding exists. In terms of closed populations the results obtained in this experiment seem to favour the thesis that less variance is found in heterozygotes than in homozygotes. This is confirmed by Scossiroli's (1953) observation that the environmental variance of the same character is decreased in lines with increased genetic variability. Similarly, Prevosti (1953) found that intra-culture variability of wing length and breadth was lower in a mass-propagated population than in an isogenic stock.

Other material on *D. melanogaster* may be found in reports by Russian workers. One particularly extensive study that may be noted here is that of Karp (1940). He carried out tests on the effect of homozygosis of segments of chromosomes of different length on daily egg production and longevity. The general conclusion that may be made from an analysis of his data is that greater homozygosity (as judged by a series of marked genes) leads to greater variability, but not all individual tests conformed to this pattern.

Thus with respect to an X chromosome carrying *sc*, *v*, *f* and *car* in a homozygous state, the average daily egg production was found to be 29·3 with a coefficient of variation of 72. Heterozygotes for this chromosome (over + + + +) had a production of 43·2 eggs with a coefficient of variation of 90, while homozygotes for wild type at these loci had a production of 24·0 with a coefficient of variation of 94. On the other hand, chromosome–III heterozygotes for *ru*, *h*, *th*, *st*, *cu*, *sr*, *e* and *ca* produced 17·8 eggs with a coefficient of variation of 122; heterozygotes 53·2 eggs with a coefficient of variation of 59, and homozygous wild type (apparently the same control was used in both cases) 24·0 with a coefficient of variation of 94.

In general, the genotypes with higher egg production and longevity, i.e. the more adapted ones, had lower coefficients of variation than those with lower mean values. The inference is clear that, although heterozygosity may be a significant factor in keeping down phenotypic variance (as shown by chromosome III), the specific adaptive value of each allele is also a contributor (as shown by the X chromosome) to variability.

The particular point can be illustrated in many other ways. For instance, heterozygotes for various position alleles involving the *cubitus interruptus* locus may show greater deficiencies in venation than either their own or wild-type homo- or hemi-zygotes (Stern, 1948), a fact contrary to the notion that heterozygotes are in general better buffered. However, such cases deal with single loci without any previous evolutionary history favouring coadaptation in heterozygotes, and are not critical for our hypothesis. They are mentioned here to emphasize the fact that specific gene action cannot be neglected even with the most fervent espousal of the theory propounded.

For *D. pseudoobscura* there is a study by Heuts (1948) on the longevity of carriers of the Standard and the Chiricahua gene arrangements of the third chromosome. He found that, while the heterozygotes are intermediate between the two homozygotes with respect to their longevity at 28–30° C, they are clearly superior at a temperature of 0–4° C. An auxiliary experiment by Wallace, reported on by Heuts in the same paper, indicated that the longevity of the heterozygotes at 25° C approached that of the superior homozygotes.

The whole problem of the type of comparison of variability to be made between heterozygotes and homozygotes is illustrated rather strikingly here. Adopting the same criterion as used by Gustafsson, we find that the ratios of the coefficients of variation of the former to the latter within each temperature is, contrary to our expectation, greater than one in four out of six comparisons possible (*ST*/*CH* vs. *ST*/*ST* and *CH*/*CH* respectively in three experiments). However, when the comparative variation between temperatures is examined, a different picture emerges. One may consider that the higher fitness of heterozygotes in nature refers to their ability to adapt themselves to the seasonal fluctuations in temperature. If this is so, the present thesis demands that the variability of heterozygotes between experiments of different temperatures should be lower than that of homozygotes. Heuts states that the diversity of conditions between the experiments at different temperatures precludes direct comparisons of means. However, this warning does not apply to the comparison of variability that we wish to make, since all three genotypes were represented in all experiments. Without replication no statistical validation is possible but the results are reasonably clear-cut.

When one compares the differences in mean longevity at three temperatures of the three genotypes, the following figures are obtained:

Genotype	*Difference in mean longevity, days*		
	(28–30)°–25°	25°–(0–4)°	(28–30)°–(0–4)°
ST/*ST*	4·57	6·11	10·68
ST/*CH*	2·02	4·19	6·21
CH/*CH*	3·01	4·57	7·58

The only curious feature here is that the *CH*/*CH* genotype, which is the poorest adapted one of the three in all temperatures, shows less variability than the other homozygote, a fact which weakens our case to some extent.

TABLE 13

Means and coefficients of variation of daily average egg production of *D. persimilis*
(Spiess, Ketchel and Kinne, 1952)

	Homozygous Whitney		*Homozygous Klamath*		*Hybrid*		*Reciprocal hybrid*	
Age	*Mean*	*C.V.*	*Mean*	*C.V.*	*Mean*	*C.V.*	*Mean*	*C.V.*
1–10 days	15·1	0·40	13·5	0·38	20·5	0·28	18·4	0·36
11–60 days	15·7	0·28	8·8	0·42	19·1	0·22	17·3	0·31
61–110 days	13·1	0·37	8·6	0·39	11·2	0·43	7·2	0·46
111–160 days	5·1	0·31	3·9	0·66	5·1	0·47	4·0	0·70

To conclude our survey of evidence from *Drosophila*, we may cite the study of Spiess, Ketchel and Kinne (1952) on egg production of *D. persimilis* females carrying combinations of the Whitney and Klamath arrangements. Their results are given in Table 13, demonstrating rather clearly that, wherever the heterozygote shows heterosis, it also exhibits reduced variability.

12. HETEROZYGOTE VARIANCE IN HIGHER ANIMALS AND PLANTS

Turning to higher animals, a detailed analysis is available for chickens in the investigation of Shultz (1952) on the variation in egg shape. He studied variance components in the length-width index of eggs laid by an open-bred population, by inbred lines and by crosses between them. Eggs laid in the first and second positions in the clutch were analysed separately. Shultz isolated the variance component (U) between eggs laid by the same bird, which represents one form of strictly environmental variance, and the component (P) between birds within inbred lines and within crosses. The latter includes equal fractions of genetic variance in the inbreds and the crosses. Hence the differences between P values for the two groups are in the environmental contributions. The values for U and P were found to be as follows:

Component	*Egg shape*	*Open-bred flock*	*Within inbred lines*	*Within line crosses*
U	Position 1	4·058	4·254	3·658
	Position 2	3·518	5·504	4·469
P	Position 1	—	4·235	3·585
	Position 2	—	4·195	3·405

These figures show a consistent confirmation of the thesis set forth here. Shultz also computed P components of two other characters in three groups of inbred lines and crosses within these groups. As shown by the following figures, the environmental variation of the crosses is once more lower than that of the inbred lines in every case:

Designation and number of lines	*Egg weight*		*Shank length*	
	Inbreds	*Crosses*	*Inbreds*	*Crosses*
2 *HEW* lines .	14·211	13·095	0·1000	0·0861
4 *EN* lines .	10·784	7·860	0·0844	0·0463
2 *LEW* lines .	8·347	4·610	0·0589	0·0351

A somewhat different example is provided by the correlation demonstrated in the data of Bernier, Taylor and Gunns (1951) between the maximum diameter of the blastoderm in unincubated eggs and the coefficient of variation. Females of three lines of breeding were used in inbred, outbred and crossbred matings, and, as shown by the rank order of the mean and coefficients of variation, the inbreds with lower average blastoderm sizes always had the highest variability:

Line	1		2		3	
	Mean	*C.V.*	*Mean*	*C.V.*	*Mean*	*C.V.*
Inbred	3	1	3	1	2	1
Outbred	2	2	1	3	—	—
Crossbred	1	3	2	2	1	2

For mammals, several examples are available. Butler's (1952) data for body weight in mice are by and large favourable to the thesis advanced, as shown in Table 14, although no heterosis in crosses was observed. The material of Falconer and King (1953) likewise suggests that relatively inbred strains of mice selected for body weight are not less variable than a cross between them. An even more emphatic confirmation is available from the 90-day body weights of rats in Livesay's (1930) experiment analysed in the manner of Gustafsson (Table 15).

TABLE 14

Means and coefficients of variation of body weight in grams of three strains of mice and the crosses between them (Butler, 1952) *L* is a strain selected for large size; *S* one selected for small size; *D* represents mass-produced descendants of an inbred line.

Strain or cross	*Males*		*Females*	
	Mean	*C.V.*	*Mean*	*C.V.*
L	33·7	9·5	30·3	8·0
S	13·1	11·0	10·8	14·9
L♂ × S♀	19·1	9·5	17·4	4·9
S♂ × L♀	22·2	13·1	19·4	14·0
L	33·6	11·8	29·1	9·6
S	13·7	21·2	12·3	12·4
D	22·4	14·7	18·8	18·1
L♂ × D♀	31·8	8·6	26·2	7·8
S♂ × D♀	20·0	8·7	16·7	10·4

There seems to be a paucity of other suitable data from laboratory mammals. Wright's (1920) classical study of inbreeding in guinea pigs included a comparison of environmental variance of piebaldness in inbred lines with that in outbred control populations. No support for our thesis can be found in this material, but there are, of course, rationalizations that can be invoked to reconcile this fact with our hypothesis (e.g. how adaptive is piebaldness?).

TABLE 15

Ratios of the coefficient of variation of 90-day body weight of hybrids (F_1) to that of inbred rats (Livesay, 1930)

Strains crossed	*Ratio*	*Males*	*Females*
S_1 and S_2	F_1/S_1	0·45	0·83
	F_1/S_2	0·47	0·62
S_1 and S_3	F_1/S_1	0·50	0·68
	F_1/S_3	0·62	0·56

On the other hand, there are data for domestic animals, such as swine, which suggest that the variance of the F_1 between inbred lines is indeed lower than that of the parents entering the crosses. A statement to this general effect may be found in the report of England and Winters (1952) and some excellent data have been supplied to me by Professor C. T. Blunn (1952) of the University of Nebraska. Table 16 summarizes the relationship between F_1 averages in body weight as well as between the average coefficients of variation of the parental lines and the crosses found in his material. With very few exceptions, lower variability of the F_1 is demonstrable in these data.

When one turns to plant material, little satisfying evidence is available. Surprisingly enough, in spite of the huge mass of material reported in the literature on the performance and variability of inbred races of corn and of crosses between them, suitable figures for testing the point at issue are extremely scarce. Apparently most of the workers took it for granted that since all the highly inbred and F_1 variance is environmental, there is no need to report it. Thus Mather (1949*b*), in the course of presenting various examples of variance partitioning of quantitative traits, records only one F_1 variance for cross-fertilized plants. It refers to corolla length in a cross between two species of petunia, where the F_1 coefficient of variation is 4·89 per cent as compared to 9·74 and 8·32 per cent for the parents. In a detailed study of another petunia species (Mather, 1950) the variability of stigma height (Table 17), as well as of the height of anthers, was found with one exception to be lower in heterozygotes than in homozygotes. Indeed, Mather states: 'Evidently the homozygous genotypes produced by inbreeding are more subject to developmental variation, less able perhaps to cope with the vagaries and chances of development, than the heterozygous genotypes of F_1.'

TABLE 16

The direction of the difference in mean body weight of swine at different ages and their coefficients of variability between the F_1 and the inbred parental lines (based on data of Professor C. T. Blunn of the University of Nebraska co-operating with the U.S. D.A. Regional Swine Laboratory). A plus sign indicates that the F_1 has a higher value than the parental average; a minus sign, the reverse

Line Number			10		11		12	
Coefficient of inbreeding (F)			0·295		0·291		0·157	
Line	F	*Age in days*	*Mean*	*C.V.*	*Mean*	*C.V.*	*Mean*	*C.V.*
8	0·400	0	+	−	+	−	+	−
		56	+	−	+	−	+	−
		154	+	−	+	−	+	−
10	0·295	0			+	−	+	−
		56			+	+	+	−
		154			+	−	+	−
11	0·291	0					−	−
		56					+	+
		154					+	+

TABLE 17

Mean squares between homozygous lines (A, B, C) and crosses between them (AB, AC, BC) for stigma height of *Primula sinensis* (Mather, 1950)

	Mean squares					
Year	A	B	C	AB	AC	BC
1946—Between plants	1·09	0·76	0·60	0·13	0·32	0·09
Within plants	0·26	0·56	0·25	0·08	0·17	0·13
1948—Between plants	1·07	0·75	0·87	1·80	0·18	0·49
Within plants	0·43	0·38	0·42	0·24	0·23	0·16

A search of the literature on corn yielded only a limited number of examples with the needed statistics given directly or in a form permitting analysis. The data, on the whole, while not in strong contradiction to our thesis, do not lend it much support. Without going into unnecessary detail, it may be noted that in two publications of Jones (1922, 1939) yield is found to vary less in crosses than in inbreds, which is also true for height of stalk in the first report. Contrariwise, in two other papers (1918, 1920) variability of crosses is sometimes lower, sometimes higher, but more generally intermediate between the variability values of the parents. The latter situation was also found in the study of Emerson and Smith (1950). Similarly, in the report of Maliani (1952), though no case of higher F_1 variance appears, the different characters were roughly equally divided between lower and intermediate F_1 coefficients of variation.

One example comparable to the *Drosophila* study of Heuts reported above was located. Harvey (1939) grew inbred lines of corn and crosses between them in several nutrient solutions differing in mineral content. The hybrids and inbreds were observed in the course of two separate experiments, but unless for some reason the variation between solutions within an experiment was different in the two, the type of comparison to be made here is legitimate.

TABLE 18

Comparative variability in total dry weight of inbred lines of maize and crosses between them, when grown in three different nutrient solutions (Harvey, 1939)

Parental lines		*Ratio of coefficients of variation*	
P′	P″	F_1/P'	F_1/P''
Mc	Hy	0·24	0·30
Mc	R4	0·02	0·05
Mc	PR	0·13	0·44
Hy	La	0·20	4·50
Hy	R4	0·98	2·05
R4	Hy	0·23	0·48

The particular point we wish to examine is whether the hybrids vary between solutions more or less than the inbreds. The computations made consist of the determination of the standard deviation of a trait around the mean for three solutions; the value obtained is divided by the mean itself, and the ratios of the coefficients of variation thus calculated for the hybrids to those of the respective inbred parents are determined. This procedure once more follows Gustafsson's method. Table 18 shows that, with two exceptions, the variability of the hybrid in total dry weight is indeed considerably less than that of the parental inbreds.

Other literature indicates that plant material is irregular in behaviour with respect to the comparative variability of inbreds and hybrids. In certain traits in some organisms reduction in variability upon crossing is evident, and in others not. The situation in self-fertilized plants is very doubtful. On the grounds which form the basis of the postulate for cross-fertilized organisms (i.e. that departure from the breeding system normal for the species leads to loss of buffering powers), the expectation for autogamous populations is that the variance of the F_1 will be higher than that of the parents. In the data examined, this prediction, as a rule, was not realized. For instance, in Malinowski's (1935) study on beans the numbers of comparisons in which the coefficients of variation of the F_1 were higher, intermediate or lower than those of the parents were, for a series of traits:

	Higher	*Intermediate*	*Lower*
Height of plant . .	0	0	4
Dry weight of vines .	2	1	1
Length of terminal leaflets	1	1	2
Number of pods . .	1	0	2
Number of seeds . .	1	0	2

Again, in wheat crosses reported by Palmer (1952) the F_1 variation was mostly in the direction of lower values (it should be noted that heterosis was observed in this case). In another wheat cross (Copp and Wright, 1952) the F_1 variation was higher or lower than that of parents, depending on whether raw or logarithmically transformed data were analysed. In tomatoes, to use one of the numerous examples available, the data of Powers (1942) show environmental variance of the F_1 with respect to fruit weight expressed in log grams to be intermediate between the parents. In Galeopsis (Hagberg, 1952) sometimes higher and sometimes intermediate variability of the F_1 was noted. Thus the variability in self-fertilizing plants does not follow an entirely consistent pattern, a fact which in itself is not of great significance to the problem under discussion, since in cross-fertilized organisms the data on the whole are favourable to the thesis advanced. The difficulties of forming an absolute judgment have been enumerated in section 10. In spite of them, if proper weighting is given to the more critical material such as is represented by the work of Dobzhansky and Wallace (1953) and some others (e.g. Robertson and Reeve, 1952*a*), the conclusion that heterozygosity reduces variability around the adaptive mean value of a character in cross-fertilized species, supported by an increasing number of investigators (see e.g. Lewis, 1953), appears to be justified.

PART III

INTERPRETATION

13. CANALIZATION AND BUFFERING

HAVING reviewed the evidence on the various points bearing on the hypotheses listed in section 2, we shall next turn to a more speculative consideration of their theoretical bases. The first of these to be discussed deals with the mechanism underlying the assumed superior buffering properties of heterozygotes.

The increased auto-regulating powers of higher organisms must be based, as Waddington (1942) has pointed out on canalization of development. In his words, '. . . developmental reactions, *as they occur in organisms submitted to natural selection*, are in general canalized. That is to say, they are adjusted so as to bring about one definite end-result regardless of minor variations in conditions during the course of the reaction.'

Indeed, Waddington finds abundant embryological and genetic evidence to support this point of view: 'It is a very general observation to which little attention has been directed (but see Huxley, Plunkett, Ford) that the wild type of an organism, that is to say, the form which occurs in Nature under the influence of natural selection, is much less variable in appearance than the majority of the mutant races.' Further, '. . . the occurrence of an adaptive response to an environmental stimulus depends on the selection of a suitable genetically controlled reactivity in the organism. If it is an advantage, and it usually seems to be for developmental mechanisms, that the response should attain an optimum value more or less independently of the intensity of the stimulus received by a particular animal, then the reactivity will become canalized, again under the influence of natural selection.'

Both Waddington and Schmalhausen (1949), who had independently elaborated similar ideas, have apparently considered that the increase in the powers of auto-regulation of development is based on such genetic properties as dominance, pleiotropy and dosage compensation, resulting from the substitution of less efficient by more efficient alleles. Presumably fixation of particular genes would be part of such a process. However, our views on the nature of genetic variation in interbreeding populations have undergone a change from the earlier idea that evolution leads to the production of genetically uniform groups. The evidence on concealed variability in natural and domestic populations compels us to view Mendelian populations as being exceedingly heterogeneous aggregates of largely heterozygous genotypes. The degree of adaptedness of individuals and of groups in cross-fertilized species then may well be a function of their degree of heterozygosity. If the heterozygotes are more adapted than homozygotes it follows, by the same chain of reasoning as was used by Waddington and Schmalhausen, that the phenotypic variation of the heterozygotes may be expected, as we postulated in the preceeding sections, to be less than that of homozygotes. Expressed in other terms, it may be said that heterozygotes are better canalized, better buffered in their developmental processes than homozygotes, or that they exhibit greater homeostatic properties. It should be clear that the basis of buffering must reside in some sort of cybernetic model, where alternative pathways are available to the organism, depending on the variation in its genetic and environmental milieux. Such models are easily enough constructed.

For example, let us suppose that in the ordinary sequence of events gene *A* produces substance *a*, which is transformed by the action of *b* (a product of gene *B*) into *r*, which in turn interacts with *c* (a product of gene *C*) to give substance *t*:

$$\begin{tikzcd}
A \arrow[r] & a \arrow[dr] & & \\
& & r \arrow[dr] & \\
B \arrow[r] & b \arrow[ur] & & t \\
& & & \\
C \arrow[r] & c \arrow[uurr] & &
\end{tikzcd}$$

or, represented in a linear fashion:

$$\begin{tikzcd}
a \arrow[r] & r \arrow[r] & t. \\
b \arrow[ur] & c \arrow[ur] &
\end{tikzcd}$$

If now, either because of mutation of *B*, or because of an environmentally produced failure to provide a substrate from which *b* can be manufactured, a block between *a* and *r* has occurred, *a* will presumably accumulate. A buffered system will be one in which high levels of concentration of *a* will interact with *d* (product of gene *D*) to produce *s*, which can be transformed by *c* into *t*:

$$\begin{tikzcd}
a \arrow[r] & s \arrow[r] & t. \\
d \arrow[ur] & c \arrow[ur] &
\end{tikzcd}$$

Thus when *a* accumulates, an alternative pathway for the organism enables it to reach the stage at which *t* comes into play. This is a genuine feedback system, since the exact course of events leading to normal character expression is determined by the 'information' that the organism has with respect to the level of *a*.

Such a model presents no difficulties if we consider genes *A*, *B*, *C*, *D*, to be the wild-type alleles. If however, we view the buffering system as a property of heterozygotes, alternative alleles at the different loci involved may need to have different functions rather than be hypomorphs or amorphs of the better adapted allele.

The view that most mutants with easily discernible effects are hypomorphic or amorphic is well justified by the evidence on their phenotypic expression and by theoretical considerations. We must therefore assume either (1) that the buffering properties of heterozygotes depend on genes differing in their behaviour from the majority of mutants studied in the laboratory, or (2) that the cybernetic model described depends, not so much on complete blockage of allele action at a given point, as on intermediate levels of production of some primary substance in the heterozygote. It is indeed possible that one form of homozygote produces too much of some material ('the safety factor'), a process leading to competition between genes at different loci for the same substratum, which in turn unbalances developmental processes.

The first alternative corresponds to the distinction between oligogenes and polygenes, suggested by Mather (1941), and discussed specifically with respect to buffering of developmental processes in an exchange of notes by Mather (1943) and Waddington (1943). It is not necessary to accept this distinction. In fact, in view of the current ignorance of the nature of gene action, a variety of possibilities seems equally likely or unlikely according to personal preference. Thus one may use such vague terms as those of East (1936), who advanced the notion that alternative alleles at a given locus have different functions; or follow Wright's (1943) idea that genes which can be ordinarily isolated involve a loss of function, while what may be called polygenic alleles at a given locus differ quantitatively; or favour Sturtevant's (1948) notion that 'wild' alleles differ among themselves in efficiency. One may assume with Robbins (1941) that heterozygotes have greater synthesizing abilities or lower specific requirements than homozygotes. One may suggest that a given gene acts in a switch fashion with respect to one trait and not with respect to another; or argue that our observations on buffering, being made on a phenotypic scale of measurement, can in any case tell us nothing about the exact process by which it is brought about. In other words, in the current stage of knowledge a wide variety of speculative hypotheses can be invoked without immediate hope of proof or disproof. This question will be returned to in section 20.

A similar situation is found in dealing with another problem raised by the hypothesis that heterozygotes are better canalized than homozygotes. The question may be framed thus: Is heterozygosity obligate for specific loci, or is it its general level (i.e. percentage of loci in that state) that is significant in determining whether an individual is well buffered or not?

Under the first condition the more or less classical viewpoint that genes at each locus have an indispensable function must be taken. Only those loci which exhibit specific overdominance will contribute to the selective advantage of homozygotes when compared to more homozygous individuals, and it is not homozygosity as such that is disadvantageous, but homosygosity of only some particular loci. If one could assess the specific action of genes at each locus and then make any of them heterozygous at will, it should be possible to reach high levels of homozygosity by maintaining only the overdominant loci in a heterozygous state.

This may be impossible even in theory if the second condition applies. If genes at many loci are interchangeable in their effects it may be supposed that an organism can afford to be homozygous at locus *A* so long, and only so long, as it is heterozygous at locus *B* (and *vice versa*). It then follows that the organism can tolerate only a certain percentage of its loci in a homozygous state. Which of the loci are heterozygous and which homozygous does not

matter here. In other words, it is heterozygosity *per se* rather than the genic contents of the individual which is the important consideration.

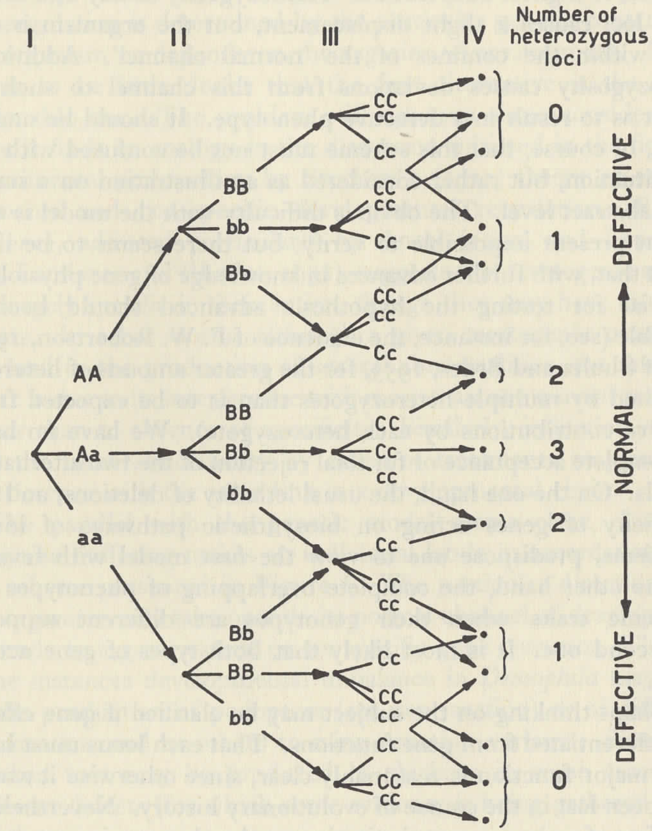

FIGURE 7. Non-specific control of buffering by heterozygous gene pairs. Roman numerals represent stages of development between which the products of gene pairs *Aa*, *Bb* and *Cc* enter into play. The arrows represent developmental paths taken by each genotype. At the extreme right the range of normal phenotypic expression is indicated.

Figure 7 is a highly schematic representation of the buffering of development by non-specific action of heterozygous gene pairs. The clear assumption made here is that gene action is not additive, the contribution made by each locus depending on the rest of the genotype. One may also say that the phenotype at the measurable level (extreme right of the figure) reflects the totality of combinations at the loci considered rather than the individual pairs of genes. Thus heterozygosity at all three loci produces the norm, or form of highest adaptedness. Homozygosity at any one of the three loci causes a slight displacement, but the organism is still kept within the confines of the 'normal channel'. Additional homozygosity causes deviations from this channel to such an extent as to result in a defective phenotype. It should be understood, of course, that this scheme must not be confused with the real situation, but rather considered as an illustration on a somewhat abstract level. The obvious difficulty with the model is that it is at present impossible to verify, but there seems to be little doubt that, with further advances in knowledge of gene physiology material for testing the hypothesis advanced should become available (see, for instance, the evidence of F. W. Robertson, 1952, and of Shultz and Briles, 1953, for the greater amount of heterosis exhibited by multiple heterozygotes than is to be expected from additive contributions by each heterozygote). We have no basis for complete acceptance or for total rejection of the two alternative models. On the one hand, the usual lethality of deletions, and the specificity of genes acting on biosynthetic pathways of lower organisms, predispose one to view the first model with favour. On the other hand, the complete overlapping of phenotypes for polygenic traits when their genotypes are different supports the second one. It is most likely that both types of gene action occur.

Perhaps thinking on the subject may be clarified if gene effects are differentiated from gene functions. That each locus must have some major function is reasonably clear, since otherwise it would have been lost in the course of evolutionary history. Nevertheless, the effect of a given gene substitution on the phenotypic expression of a polygenic trait may be of exceedingly minor character. In a sense this is a reconciliation of the two models (as is found for instance in Emerson's, 1948, case of a balance between competitive systems in the relation of sulfonamides to p-aminobenzoic acid in *Neurospora*). Further speculations on this particular point would not be very profitable. The main fact is that models for obligate heterozygosity as a mechanism of developmental canalization are readily enough constructed to provide a theoretical basis for the data given in sections 11 and 12.

14. SPECIFICITY OF UNBALANCE

THE question may be asked whether the type of phenotypic unbalance produced in consequence of failure of developmental self-regulation is determined by the particular genetic contents of the organism or depends on the vagaries of environment. There seems to be little doubt that the first alternative is the more reasonable one. The problem still deserves some consideration since it finds an analogy in the discussion initiated in the field of experimental embryology by Stockard's (1921) theory of critical moments and non-specific developmental retardation. Recent evidence, adduced particularly by Ancel (1950) and Landauer (e.g. Landauer and Rhodes, 1952), suggests that teratogenic agents are largely specific in their action, though they may have multiple effects. In other words, although a given teratogenic treatment can lead to the production of several abnormalities, the multiple effect is due to its interference with more than one normal reaction rather than to absence of specificity. Similarly, induction of one and the same abnormality by different treatments may involve interference with the same link in a developmental chain.

The parallel with the genetic model seems clear. Lack of adequate buffering makes an individual labile in accordance with the scheme presented in Figure 6. The particular direction that the organism may take outside its normal channel of development depends to a great extent on its specific gene contents. Thus in some instances developmental unbalance in *Drosophila* may lead to the production of podoptera (see next section) or of different homoeotics, and in others to wing-venation variants. Similarly, crooked toes may be produced in chickens in some cases and different defects (for which some evidence is being gathered now) in others.

However, a variety of genic constellations may be switched to the same developmental route by the presence of appropriate environmental stimuli at a given point in ontogeny. Furthermore, by selection it is possible to 'purge' lines of the particular genes producing the phenotypic deviation, without necessarily regaining a balance. Thus in the reverse selection of the crooked toes lines of chickens (table 4) continued inbreeding produced individuals theoretically more homozygous (and hence, according to our hypothesis, less buffered) than those in the direct selection, but lacking the defect. The difficulty in reproducing this line argues for the view that a genetic balance was not attained in these birds. In spite of their non-optimal genetic constitution, their phenotype was normal. It is possible that actual development followed a course different from that of balanced individuals but resulted in the same phenotype (Dalcq's, 1941, *teleogenetic paragenesis*).

It is in the light of such a concept that Waddington's (1952) experiment on production of phenocopies may be interpreted. The experiment consisted of subjecting *Drosophila* pupae to a temperature shock which produced about 40 per cent crossveinless individuals. To quote: 'Two selection lines were set up, in one of which the flies which showed the phenocopy were bred from in each generation, while, in another, selection was against phenocopy formation. Fairly rapid changes were produced in both directions', the phenocopy-susceptible line reaching a level of over 90 per cent by the 19th generation, and the resistant line at the same time dropping to about 10 per cent incidence. At the 12th generation crossveinless flies began to appear in the susceptible line without the application of shock.

It is possible that the real object of selection in this experiment was stronger or weaker buffering. The genetic basis for this possibility is suggested by the examples cited by Timofeeff-Ressovsky (1940), such as the gene in *D. funebris* which in homozygous form changes the number of thoracic bristles in either one or the other direction, depending on the individual carrying it. The particular appeal of the experimental technique used by Waddington lies in the fact that, if it is repeatable, a variety of tests to verify whether heterozygosity does indeed confer superior buffering abilities immediately suggests itself.

Other evidence on the general subject is furnished by such experiments as have been carried out by Landauer (1947) on the susceptibility of chicken embryos to insulin induction of abnormalities. The example of significance to us lies in the comparison of defects induced in his *homozygous polydactylous* stock with those in the *short upper beak* selected stock. The latter originated from the former by selecting for 'modifying genes' which suppress the 'lethal action as well as the morphological consequences' of the short upper beak mutation (*su*), first found in the polydactylous stock. The following table gives the incidence of defects in the two stocks, when two units of insulin are injected into eggs prior to incubation:

Stock	*Units of insulin*	*Percentage rumpless*	*Percentage beak abnormalities*	*Percentage other malformations*
Polydactylous	0	0·8 ± 0·8	1·7	0
	2	35·2 ± 5·7	8·5	4·2
Selected short beak	0	0·8 ± 0·5	24·0	0
	2	13·4 ± 2·5	43·3	1·6

Apparently, selection for modifiers of the expression of the short upper beak gene also resulted in buffering the embryos against insulin-induced rumplessness. In other words, buffering is not necessarily entirely specific at the phenotypic level. Landauer's earlier (1945) suggestion was that 'the primary function of the modifiers is that of protecting the organism against agencies which tend to push the course of its development into dangerous channels.' In view of the above evidence, he now considers that beyond the primary function of specific protection, modifiers 'may play a more general rôle in safeguarding against damage (from hereditary or external agencies) to structurally or functionally related systems.' It is this very rôle that we wish to assign to heterozygosis.

It must be understood that this suggestion does not necessarily apply to Landauer's own material; in addition to heterozygous buffering genes, recessive or dominant modifiers of self-regulation may exist. Some light on this point is thrown by Landauer's (1948*a*) experiments on the effect of insulin injection on the expression of polydactyly. He found that Dorking fowl, which are homozygous for the polydactylous condition, are better protected against insulin-induced developmental disturbances (as measured by the degree of asymmetrical expression) than heterozygous or 'outbred' stocks homozygous for this gene. His observations, however, do not negate the possibility of heterozygosity as a buffering mechanism in other cases. In fact, the particular reason for discussing his material here is to demonstrate the existence of buffering genes, regardless of whether their action is of significance to the embryo in the homozygous state only, in the heterozygous state only, or in both cases.

Landauer (1948*b*) also summarized some aspects of the genetic behaviour of skeletal abnormalities. He notes that 'Heterodactylism is a common phenotype among heterozygotes but is rare in homozygotes. Complete suppression of the polydactylous condition also occurs much more commonly in heterozygous animals.' The first sentence of the quotation suggests poorer regulation in heterozygotes; the second better. A comparison between the Jungle fowl and the Leghorn breed is made in the same study, the following being the percentage incidence of abnormalities as a result of injection of 5 units of insulin at 120 hours after incubation:

Male	*Female*	*Micromelia*	*Beak abnormalities*	*Eye abnormalities*
Leghorn	Leghorn	87·3 ± 1·8	39·2 ± 2·7	4·3 ± 1·1
Jungle	Leghorn	78·7 ± 2·7	31·3 ± 2·1	3·0 ± 1·1
Leghorn	Jungle	96·2 ± 1·3	35·7 ± 3·1	8·9 ± 1·9
Jungle	Jungle	96·5 ± 2·0	62·4 ± 5·3	9·4 ± 3·2

The Jungle fowl is not protected here as it is when injection is made before incubation (incidence of rumplessness being 28·0 ± 1·5 per cent in Leghorns and 9·3 ± 2·9 per cent in Jungle fowl). However, since the eggs of the latter are smaller, they received a higher relative dose of insulin, so that, in reality, there may be no difference between the breeds in this series. Landauer says: 'The relatively low incidence of beak abnormalities in both crosses may be a result of heterosis,' i.e. that heterosis is indeed a buffering mechanism.

15. GENETIC BASIS FOR PHENODEVIANTS

We may now return to a further consideration of phenodeviants, with particular reference to podoptera and to Dubinin's interpretation of the genetics of extra venation.

Podoptera (Goldschmidt, Hannah and Piternick, 1951) is a genetic effect which changes the wing into a leg-like appendage. Goldschmidt and his students found that the complex for podoptera is present in almost all *Drosophila* stocks and can be isolated. Goldschmidt (1949) suggested that the inheritance of podoptera (*pod*) is based on polygenes which, as postulated by Mather (1941), are resident in heterochromatin. Whether heterochromatin or euchromatin is involved need not concern us at this point. The important aspects of this character, shared by the phenodeviants already mentioned (sections 7-9), are:

1. The abnormalities appear in many strains of the respective species in a relatively low frequency.
2. They can be isolated, in the sense that strains with increased incidence at characteristic levels can be established presumably by selection.
3. They are controlled by genetic complexes, involving genes that are not always readily located.
4. Even when single major genes producing the effect are identifiable, the particular expression of the character and its behaviour in crosses depends on a system of polygenic modifiers.

There are a number of other features common to the various phenodeviants, although not enough evidence has been presented to determine whether all of these occur in each case. For instance, podoptera lines, like the crooked-toes line in chickens in its early stages of development, encounter difficulties in reproduction under persistent selection for increased incidence (lowered fecundity and viability). Again, the incidence of crooked toes seems to increase under adverse incubation conditions (as measured by percentage hatchability), and the frequency of otocephaly in guinea pigs may be expected to behave in an analogous fashion under Wright's hypothesis that a general depression in a vital activity at the critical moment of development brings about this defect.

There is but little doubt that the specific gene contents of the affected stocks is to a great extent responsible for the differences in the frequency with which the abnormality is manifested. At the same time it is rather striking that 'isolation' of podoptera (as in the other cases cited) is in all instances synonymous with inbreeding. As a matter of fact, the concepts of selection and inbreeding are used by Goldschmidt *et al.* interchangeably. Thus on p. 155: 'Penetrance was further increased by making the stock isogenic, which amounts to a quick selection experiment.'

It thus appears that the behaviour of the phenodeviants does indeed resemble greatly the less specific phenomena which have long been referred to as inbreeding degeneration. It is true that Wright has stated in connexion with otocephaly that 'inbreeding *per se* does not bring about abnormal development.' Yet his grounds for this statement seem to be based solely on the failure of appearance of the monsters in one branch of an inbred stock. If we consider, in accordance with the discussion in the previous section, that the particular type of manifestation of inbreeding effects is related to the genic contents of the stock, Wright's comment does not form a serious objection to the view expounded.

Goldschmidt *et al.* have listed (p. 278) 17 features characterizing the inheritance of podoptera. The first 9 of these present a very good formulation of the expected behaviour of podoptera stocks on the assumption that the trait is controlled by the level of homozygosity, modified by differences in particular gene contents between different stocks:

1. The ubiquity of genetic factors for the *pod* effect. (The effect should have been selected against to some extent, even with low penetrance in natural populations.) Hence, a reasonable proportion of isolates would be expected to be *pod*-free. If *pod*, however, is an inbreeding effect, it should be observed in most populations limited in size, irrespective of phenotypic selection against it.
2. The grading of penetrance, and
3. The presence of *pod* factors in all chromosomes (to be expected on the inbreeding hypothesis).
4. The production of many different phenotypes which are typical for each line (the unbalance in development produced by excessive homozygosity is general; the precise expression varies with genetic content).
5. The collaboration of these factors as a multiple-factor system within each line (to be expected, since the incidence of the effect would be related, at least over a part of the range, to the number of accumulated homozygous segments).
6. The lack of allelism between the *pod* factors of different lines (the homozygous segments would be different in different lines).
7. The lack of multiple factor collaboration between lines.
8. The pseudoallelism between *pod* factors.
9. The pseudoallelism between *pod* and factors in different strains of dominant mutants (all three to be expected if combinations of different lines represent heterozygotes).

The remaining 8 features refer either to the behaviour of particular stocks (analogous to such special cases as the single gene which increases otocephaly incidence in one of Wright's sub-branches of guinea pigs), or to factors the relevance of which to the validation of the suggestion made here is not immediately apparent.

It will be clearly recognized that our general hypothesis recalls, as we have already had occasion to remark, the pre-Mendelian notions about the effects of inbreeding. With the discovery of Mendelian heredity the opinion held by earlier investigators that inbreeding *per se* is harmful was abandoned in favour of the idea that the gene contents alone determined the phenotype of the homozygote, inbreeding in itself being neutral in its effects. It seems as if the pendulum may have swung too far in that direction and that a partial return is justified, as it was in so many cases (e.g. in population genetics of quantitative traits, founded on the synthesis of Mendelism with at one time disreputable biometry). The evidence being accumulated on the rôle of overdominance in fitness (section 5) and in evolutionary processes (e.g. Vetukhiv, 1953), and particularly on the selective advantages of multiple over single heterozygotes (F. W. Robertson, 1952; Schultz and Briles, 1953), appears to make such retracing of steps mandatory at this time. Not only gene contents but homozygosity as such must be considered to play a rôle in inbreeding degeneration.

The basic conclusions reached by Goldschmidt *et al.* are affected by our hypothesis only to the extent to which one desires to question their evidence on the significance of intercalary heterochromatin in the podoptera effect, while the polygenic concept adopted from Mather is not changed.

The implications of the general viewpoint presented here have wide evolutionary significance. They have been elaborated in part by Dubinin (1948) in connexion with his study of extra venation. It may be best to give translated excerpts from his discussion.* Dubinin, referring to the evidence summarized in section 8, states: 'All these peculiarities demonstrate that the reason for the existence and origin of the hereditary system determining extra venation can lie only in the action of natural selection. The object of selection is a definite heterozygous state of the hereditary system which insures the optimum expression of physiological adaptation, the external manifestation of which is variability in extra venation. Because of the polygenic nature of the inheritance of this trait, the action of selection is directed towards the creation of a stabilized and harmonious gene complex. The necessity for supporting this complex in a heterozygous state has determined the peculiar features of its evolution in the shape of polygenic organization within the limits of one chromosome. The ubiquity of this heterozygous system shows that in this case adaptive polymorphism is not a response to local conditions, but represents physiological heterosis of general significance to the species.'

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* Professor Carl Epling of the Department of Botany, University of California at Los Angeles, has made it possible to obtain at cost price from the Library of his institution copies of a translation of the whole article.

Further: 'As has already been pointed out, the evolution of stabilization of heterozygosity of the hereditary system for extra venation led to the organization of polygenes within the limits of one chromosome. Maintenance of heterozygosity in this case is impossible without segregation of homozygotes. Therefore, the most advantageous condition is one where part of the polygenes is located in one and part in another homologous chromosome. Such organization of polygenes interferes with their free recombination, since homozygotes can appear only after crossing-over. Thus, since union of a crossover chromosome burdened by a complex of polygenes with another chromosome, having a partially optimal set of polygenes, leads to the appearance of traits which reduce viability, there are obstacles to complete segregation of homozygotes, in the shape of selection acting on the intermediate phases of character manifestation. However, a certain movement along the scale of different polygenic complexes—dynamic changes of the system under the influence of selection—occurs in nature, as we have seen in the example of the seasonal cycle, and as possibly also happens under different ecological conditions. In this manner the system as a whole carries within it definite elements of stabilization, and simultaneously possesses great plasticity.

'We see here that the whole species is maintained in the state of constant heterozygosity without the presence of special adaptations such as chromosome aberrations balanced by lethals. This shows that selection coefficients in this case must be considerable.'

And finally: 'The facts of intra-population heterosis point to the general significance of heterozygosity for the life and evolution of populations. Investigations of *Drosophila* populations have shown that normal viability is, as a rule, based on heterozygous structures. When individual chromosomes taken from completely viable individuals are made homozygous, we nearly always obtain a marked reduction of viability. One should not, of course, become attracted by mystical hypotheses about the harmfulness of homozygosity in general. In our studies (Dubinin, 1940) on the Kutaisi population we have obtained up to three per cent of lines homozygous for the entire second chromosome which were more viable than the heterozygotes. In our work on inbreeding and fecundity in highly inbred lines (60 generations of brother × sister mating) we obtained an array of lines which exceeded in fecundity the parental heterozygous lines from nature (Dubinin, 1947). On the whole, however, inbreeding, of course, leads to a sharp drop in viability, fecundity, and other characters. The data on the significance of intra-populational heterosis indicate that the evolution of populations in many ways is based on the utilization of heterozygous structures. Evolution is directed towards the more favourable combinations of different heterozygous gene complexes. Under these conditions, the basis for such concepts as the "normal" chromosome disappears. Homozygous chromosomes as a rule do not produce a normal adapted phenotype. The optimally adapted phenotype appears on the basis of heterozygous genotypes. The very concept of "normal" phenotype assumes a dynamic character.'

'There is no doubt that phenomena of this kind (extra veinlets) are widely distributed, though as yet they have not attracted sufficient attention on the part of investigators.

'The presence of such dynamic genic complexes creates a basis for reversible genotypic changes in populations and for remarkably rapid processes of directed changes. The maintenance of a genic complex on a particular level is based on heterozygosity; therefore, as it has been shown above, populations have the constant possibility for both sharp drops and sharp rises in the number of given genes. The changes in the plus and minus directions have a phenotypically directed character. They proceed towards a decrease or an increase in the number of extra veinlets in the wing. Using Waddington's (1942) term, development here is canalized. With changes in environmental conditions, adaptation may require the particular level of the genotypic base which will lead to the "network" type of change. We shall then have a remarkably rapid reaction of the species as a whole, which, on the basis of accumulation of a definite heredity manifesting itself in a canalized system of development, will in the course of several generations undergo the morphological evolution of the entire organ and of a series of physiological properties.'

It must be admitted that Dubinin's contention that an integration or synthesis of a polygenic system has been attained in his material rests on somewhat tenuous grounds. This fact in itself does not constitute disproof of the general basis of the genetic behaviour of phenodeviants advanced by him.

It is indeed possible that some major genes are involved in the mechanism (see the discussion in section 13). It is obvious, however, that their expression appears to be dependent on the accumulation of modifiers which are so widely scattered in natural populations as to make the potentiality for this trait ubiquitous. The relation of the modifier systems to developmental homeostasis is emphasized by a commonly observed increase in penetrance or expressivity of homoeotic mutants under unfavourable conditions (e.g. hexaptera in Herskowitz's, 1949, study). In other words, these traits exhibit poor buffering connected with increased homozygosity. Thus table 33 in Goldschmidt, Hannah and Piternick (1951) clearly shows that variation of expression increased with continual inbreeding. While a rise in level of incidence under these circumstances could be easily explained in ordinary Mendelian terms, increase in variation must be referred to failure of a homeostatic mechanism.

Great variability of expression in phenodeviants is found not only between individuals but also within individuals, so that right-left asymmetry appears rather commonly. Goldschmidt (1946) has constructed a model for this type of variability in terms of thresholds and developmental age. Irrespective of the physiological basis for this phenomenon, the important fact that is suggested by intra-individual variation is the lability of the organism endowed with genetic potentialities for phenotypic deviation. This indeed may be considered as an added point of strong evidence for an interpretation based on developmental homeostasis.

Basically, irregularly manifested asymmetry must be considered as an indication of partial failure of self-regulatory properties of an organism in the course of its ontogeny. The issue is whether poor buffering is the result of homozygosity *per se*, of specific gene (or chromosome) action, or of a combination of these effects, as is being asserted in the hypothesis here presented.

It must be admitted that, taken point by point, either of the first two alternatives can be supported as valid, but the total weight of evidence strongly suggests that the third possibility is the correct one. While still belonging more to the realm of speculation than to that of incontrovertible fact, it appears at this stage of knowledge to be the most likely explanation of the phenomena observed.

16. RELICT HOMEOSTATIC TRAITS

There is one further feature of Dubinin's investigation that should be noted. He and his collaborators found extra venation to be present not only in *D. melanogaster* but also in a number of other *Drosophila* species, and in fact throughout the whole order of Diptera. His interpretation is that the trait is of ancient standing, and that its recurrence is an atavistic manifestation. The heterozygous system of homologous polygenically determined phenodeviants may thus represent a phylogenetic carry-over from a common source, adaptive for populations as well as for individuals.

On a somewhat more modest time-scale, a parallel situation may be demonstrated in chickens. In intensively inbred lines apparently polygenic traits not characteristic of the breed often appear. It is exceedingly likely that these traits represent relicts of heterogeneous polygenic systems concerned with self-regulation.

A prime example of this kind is provided by broodiness. Under natural conditions a certain level of broodiness is necessary for reproduction. On the other hand, broodiness in chickens under domestication, when the task of incubation is taken over by machines, is undesirable, since its manifestation in a hen decreases the active period of egg production. In this sense it is an atavistic trait, towards the extinction of which artificial selection has been applied in many breeds. In spite of this fact, there is probably no flock of chickens in existence in which broodiness does not occur. It may be thus suspected that some of the genes for broodiness form part of a more general genetic complex involving balance and fitness.

There are no adequate data on relative fitness as such of broody and non-broody birds, largely because few breeders are interested in propagating the former. There is, however, reasonably clear-cut evidence that at least one component of fitness, viability, is negatively correlated with broodiness. The most complete information on this point has been provided by Byerly and Knox (1942), who also cite some preceding studies. Table 19 gives the general summary of their data.

It may be noted that in every group compared the viability of the broody birds was higher than of non-broody ones. In addition a negative regression was observed between groups of birds: for each per cent increase in the incidence of broodiness in a group, viability decreased by about one-quarter per cent (the regression was computed for sub-groups of each breed representing different generations).

TABLE 19

Percentage survival from July to October of yearling hens of different breeds

(Byerly and Knox, 1942)

	Non-broody birds		*Broody birds*	
Breed	*No.*	*% survival*	*No.*	*% survival*
R. I. Reds	951	83·8	251	90·0
R. I. Reds (inbred)	935	80·6	193	89·6
Light Sussex	282	81·9	259	93·4
W. Wyandottes	280	71·4	104	84·6
Crossbreds	751	81·9	562	91·6
Total	3199	81·2	1369	90·9

Another indication that broodiness may be associated with higher fitness is to be found in the observation of Bernier (1952) that broody birds produce eggs of higher specific gravity than non-broody ones. Since specific gravity is correlated with hatching power of eggs and the viability of chickens produced from them (Munro, 1942), this phenomenon may be interpreted in the same manner as the relationship between broodiness and viability.

Shell colour is another relict component of a homeostatic control of fitness, or at least is related to it. The ancestors of the domestic fowl laid eggs with coloured shells. The domestic White Leghorn breed, however, lays largely white eggs, though most flocks have a low incidence of birds laying creamy or tinted eggs at some time. It was discovered by McClary (1952) that such birds also tend to produce eggs of higher specific gravity than their flock-mates. This observation was confirmed by Bernier (1952)

There is another point of interest in connexion with shell colour applying to the so-called heavy breeds, which ordinarily lay eggs of varying shades of brown. Godfrey (1947) observed that the hatchability was positively correlated with the degree of shell pigmentation, so that at first sight a direct confirmation of the idea presented here seems to be available. However, Funk and

Forward (1949), while verifying Godfrey's findings, suggested that the correlation was not a direct one, but that both hatchability and shell colour are negatively correlated with egg production. The following table is submitted in support of their interpretation:

Characteristic colour of shell of New Hampshire females	*Winter egg Production*	*January-August egg production*	*Percentage hatchability*
Dark	55·0	82·1	76·9
Medium	65·5	95·9	68·3
Light	67·8	90·8	56·7

Since ordinarily the correlation between egg production and hatchability is positive (e.g. in Dempster, Lerner and Lowry, 1952) these data make the full interpretation of the situation difficult. It is apparent that some balance of fitness involving two or all three of the traits considered (production, shell colour, hatchability) exists, but determination of its exact nature will have to await a more detailed study.

17. MODEL OF GENETIC HOMEOSTASIS

So far, our consideration of the rôle of heterozygosity has been largely directed to the individual level, that is to say, to the problems of developmental homeostasis. We may now turn to a discussion of the factors operating at the level of populations, with particular reference to the phenomenon of genetic homeostasis, which, as it may be recalled, was defined as the tendency of a Mendelian population as a whole to retain its genetic composition arrived at by previous evolutionary history.

The prime evidence for the existence of such a property comes from the observed antagonism between artificial selection directed towards an extreme, and natural selection. The notion that the latter favours a balanced combination of traits is fairly old. Thus, following Darwin, Galton (1883) recognized the difficulties of obtaining major shifts in the mean of individual traits in populations of humans and domestic animals, if thereby a lack of balance between the characters under selection and other properties was created. Speculations regarding the fact that nature seems to favour the mean have been made by many writers, and some models, previously noted, have been investigated to account for the genetic mechanism involved. Before presenting here a model based on obligate heterozygosity for maximum individual fitness, which, as a by-product, leads to genetic homeostasis, some more general comments on the subject may be made. They refer in particular to (*a*) the rôle of sexual reproduction in determining population properties, and (*b*) such differences between natural and artificial selection as have a bearing on the problem.

Sexual reproduction and Mendelian heredity made possible by it have been generally viewed as progressive forces in evolution. The advantages of sex in the evolutionary process were recognized before Mendelism was discovered (e.g. by Weismann). In the more recent literature, we may note that Wright (1931) suggested that sexual reproduction by itself provides too much plasticity, and sought to determine the nature of various other evolutionary forces which would damp the excessive flexibility conferred by it on a population. Fisher (1930) pointed out that a sexual organism with only two genes could respond to natural selection at a rate approximately double that of an asexual competitor. Muller (1932*a*) viewed sexuality as the means for utilizing the possibilities of gene mutations to the fullest extent. Dobzhansky (1941) stated that sexual reproduction increases the evolutionary potentiality of a species by increasing the area of the field of genetic combinations available and thus the chance of discovering a new adaptive peak. Huxley (1943) ascribed to sexuality the capacity to form new genetic combinations permitting alteration of species when needed by utilizing already existing genetic variability. Stebbins (1950) emphasized the sheltering of recessive variation made possible by diploidy and sexual reproduction.

Basically, all these statements declare that sexuality confers plasticity on a population, and thus facilitates the transformation of the genetic composition of a population in response to changing environment. There is little doubt that this is an entirely valid view when long-range aspects of evolutionary history are concerned.

At the same time it should be recognized that sexual reproduction is also a stabilizing force, conservative in its action when short-time phenomena are considered. This idea seems quite clear when it is recalled that it is sexual reproduction that accounts for the Hardy-Weinberg equilibrium.

It is the conservative aspect of the effects of sexual reproduction that is of importance to one interested in producing directed genetic changes in a population, that is to say, to an animal breeder, even though to an evolutionist this feature represents a minor factor. To start with, all domestic animals are sexually reproduced. Should a new useful mutation occur and be identified, increases in its frequency cannot be obtained as rapidly as under asexual reproduction. Similarly, deleterious recessives are not easily eliminated. Offspring of individuals possessing a highly desirable combination of polygenically determined traits under sexual reproduction regress towards the mean of the population. In general, sexual reproduction is the basis of genetic homeostasis, and inasmuch as this phenomenon by and large operates in the direction opposite to man's efforts, it becomes, at least from a narrow view of the matter, a conservative force. It is true that genetic homeostasis, as visualized here, permits a gradual reconstitution of balanced genotypes with desirable properties. Yet, to a breeder impatient with an apparent lack or with slowness of progress in some single phenotypic trait, sexual reproduction appears inimical to his immediate interests.

In general, the contrasting views of evolutionists and breeders on the subject are to some extent reflections of the differences between natural and artificial selection. The former is usually entirely phenotypic; the latter may also be genotypic. Hence, artificial selection can be more accurate. In addition, artificial selection can address itself (or so at least most breeders assume) to isolated traits, whereas natural selection operates on the totality of all phenotypic characters affecting fitness. Artificial selection can take into account not only the magnitude of contribution that each component trait makes to the aggregate desideratum, but also the heritabilities and genetic correlations between them. This again, as shown by Lerner and Dempster (1948), can make artificial selection potentially more effective than natural selection. Finally, natural selection may involve intra- as well as inter-specific competition, the latter being absent in the course of ordinary pursuits of breeders of domestic animals.

These comparisons refer to selection as it occurs in nature and to selection which the breeder applies under domestic conditions. But, of course, artificial selection unaccompanied by natural selection is hardly ever realized in practice (except perhaps when single locus differentials, e.g. certain comb types in chickens, are involved in breed formation). In addition to whatever criteria of selection that are used by the breeder, nature maintains its selection pressure for fitness. Whenever the net effect of the breeder's efforts also leads to increases in fitness, the two pressures operate synergistically. At other times (except, as will be shown, when natural selection within certain limits of gene frequencies may be neutral in its effects) the forces are antagonistic.

On *a priori* grounds one may expect the latter situation to be more frequent than the former, because the previous evolutionary history of a population has led it to assume a composition in which fitness is already at its maximum. Introduction of new selection pressures for complexes of polygenes scattered throughout the chromosomes of the genome is bound to have an influence on frequencies of polygenes affecting fitness. The only possible direction of this influence is the negative one, since we assume that artificial selection is initiated at the optimum constitution of a population.

This fact was realized a long time ago by, among others, Kemp (1929), who stated that 'Barring mutation in random-bred forms, man is able to effect and maintain germinal improvement by selection to the extent that he utilizes the margin of variation between reproductive ability and productive ability within the environment in which the form is grown.' The counter-argument that domestic conditions are different from the environment for which the genetic composition of the population was optimum has some validity. However, the only effect that this fact may have is to postpone the origin of the antagonism between artificial and natural selection.

There are many speculative models for genetic homeostasis that may be constructed. The means for precise experimental verification of any of them are still rather limited. In spite of this fact, it seems desirable to investigate the possibility of having a model which, on the basis of a limited number of assumptions, can satisfy the evidence that has been reviewed. The following is presented with this end in view.

The three important features of the model proposed are:

1. Metric characters subjected to selection experiments behave in an additively genetic fashion.
2. Fitness as a whole exhibits the phenomenon of overdominance.
3. Polygenes affecting continuously distributed traits are organized in blocks.

The first point must be taken only as an approximation. Although, for instance, Lerner and Hazel (1947) suggested that the agreement between results and expectation on the basis of additive gene action in a selection experiment for increased egg production was exceedingly close (see also Lerner, Cruden and Taylor, 1949), more complete analysis of the data indicates that the gains obtained probably fell somewhat short of those expected (Dempster, Lerner and Lowry, 1952).* The margin of difference between gains expected and gains realized will be referred to later.

In connexion with the second point, it should be noted that the form in which the subsequent discussion is presented makes it appear as if pleiotropic action of every allele is assumed, with effects on both metric traits under selection and fitness. This is not a necessary part of the assumption made. Each of the loci to be considered may be viewed as a polygenic block containing several genes with individual effects only on some metric trait or on fitness (possibly through an effect on an unrelated trait), and, as a block, having total net effects on both. Whether it is such linkage or pleiotropy in the narrow sense that is involved, the effect of a genotype on fitness may be a secondary one acting by way of the phenotype for the metric trait. In other words, the basic assumption reduces itself to the premise that maximum fitness obtains under intermediate rather than extreme phenotypic values of other traits. This fact forms one of the fundamental principles propounded, namely, that the optimum genotype, from the standpoint of natural selection (for fitness), does not coincide with the optimum genotype from the standpoint of artificial selection (for extreme values of a given character).

The third and final point is not necessary to explain the cessation of response to selection and the relapse of the population to its original genetic composition when selection pressure is suspended. It is, however, necessary to account for renewed responses to selection after a plateau period.

The model can be presented in terms of general algebraic expressions, but the use of arbitrary values, where numerical rather than symbolic comparisons are possible, makes it easier to visualize its basis. A scheme will therefore be presented first with specified selected values for the various constants involved, and then broadened by the use of other examples together with some generalized expressions.

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* See also the criticisms of Kyle and Chapman (1953) directed at the study of Lerner and Hazel.

Assume that trait *X* is determined entirely by additive gene differences at two loci (either single genes or blocks), so closely linked that no crossovers occur. The double homozygote *aabb* is given the value of 0; each substitution of *A* for *a* adds two units to the value of *X* and each substitution of *B* for *b* adds one unit. Thus *X* can take on values ranging from 0 for *aabb* to 6 for *AABB*. Superimposition of an environmental source of variation does not in any way alter the basis of the model. The conditions governing fitness are taken to be such that the respective reproductive rates of the different genotypes are:

AA	1·0	*BB*	1·0
Aa	1·1	*Bb*	1·2
aa	0·8	*bb*	0·6

The following table gives the values of *X* and the relative reproductive rates of all possible genotypes, on condition that the joint expressions for fitness at the two loci are products of the appropriate values of each:

Genotype	*Relative reproductive rate*	*X*
1. *AABB*	1·00	6
2. *AABb*	1·20	5
3. *AAbb*	0·60	4
4. *AaBB*	1·10	4
5. *AaBb*	1·32	3
6. *Aabb*	0·66	2
7. *aaBB*	0·80	2
8. *aaBb*	0·96	1
9. *aabb*	0·48	0

Now if we assume that the original population has *A* and *b* linked in the repulsion phase, it will contain only three genotypes:

Genotype	*Relative reproductive rate*	*X*
Ab/Ab	0·60	4
Ab/aB	1·32	3
aB/aB	0·80	2

The relative reproductive rates of these three genotypes can be designated as:

Ab/Ab	$1 - s$
Ab/aB	$1 - ks$
aB/aB	1

Without other selection than is implied by these rates the equilibrium frequency of the chromosome carrying the combination *aB* will be: —

$$q_{aB} = \frac{1-k}{1-2k},$$

$$\text{while } q_{Ab} = -\frac{k}{1-2k}.$$

With $s = 0{\cdot}25$, and $k = -2{\cdot}6$ (as can be readily ascertained from the table of relative reproductive rates), q_{Ab} will be 0·42. The composition of the population at equilibrium will then be:

Genotype	*Frequency*
Ab/Ab	0·1764
Ab/aB	0·4872
aB/aB	0·3364

The mean value of *X* in this population will be 2·64 and the average reproductive rate (relative to the values given under our original assumption) will be 1·02.

If now selection for *X* is applied, it becomes possible to increase the average value of *X* to its maximum of 4, but only at the cost of reducing the relative fitness of the population from 1·02 to 0·60. If sufficient numbers of offspring can be obtained from the *Ab/Ab* individuals it is possible to produce a true breeding population averaging 4 with respect to *X*. The rate at which this composition of the population will be approached depends, of course, on the reproductive potential of the *Ab/Ab* genotype. The major penalty attached to the attainment of the homozygous population lies in the fact that no further improvement is possible, so that the maximum value *X* of 6 (for a population consisting entirely of *AABB* individuals) can never be realized, the alleles *A* and *b* being fixed.

If, on the other hand, a relative reproductive rate of 1·00 is necessary to maintain the population, the situation changes to a considerable extent. Since the *Ab/Ab* individuals alone cannot fulfil this requirement, it becomes necessary to use some *Ab/aB* individuals as parents. The proportions of the two types needed for maintaining the required level of fitness are:

Ab/Ab	0·44
Ab/aB	0·56

The offspring of a parental group of this composition will contain the three genotypes in the proportions:

Ab/*Ab*	0·5184
Ab/*aB*	0·4032
aB/*aB*	0·0784

The mean of this population with respect to *X* will be 3·44 and constant selection of parents (in the proportions specified above) will be required to maintain it at that level. If selection for *X* is relaxed, the population mean will relapse to the original level of 2·84. Contrariwise, attempts to increase the frequency of *Ab*/*Ab* genotypes in order to raise the mean to the level of 4 will always be accompanied by loss of fitness.

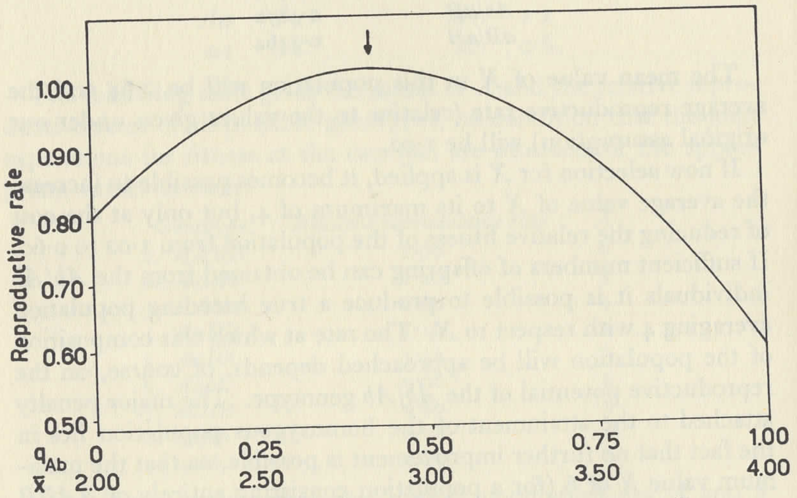

FIGURE 8. Model of genetic homeostasis ($s = 0{\cdot}25$; $k = -2{\cdot}6$)

The situation is illustrated in Figure 8. It may be seen that the maximum fitness in the population whose characteristics we have described is at the point where *X* has a mean value of 2·84, corresponding to q_{Ab} of 0·42. Under selection for *X* the tolerance limits, should we define them as the range of fitness above 1·0, are approximately 2·60 and 3·05. Transgression of these limits in either direction leads to a reduction in population size, while suspension of selection for *X* results in natural selection restoring the optimum level. The subterfuge of selecting specific proportions of phenotypes with *X* values of 4 and 3 to maintain constant population size will, as noted above, alleviate the situation only partly.

This model shows that the operation of genetic homeostasis even in traits under additive genetic control leads to the establishment of a plateau below the maximum possible expression of a selected trait, and calls for continuous selection to prevent a relapse.

At this point, before a discussion of conditions under which the ceiling *X* imposed by homeostatic forces can be broken through, the effects of variation in the values of *k* and *s* on the model constructed will be considered, using a single locus for the sake of simplicity.

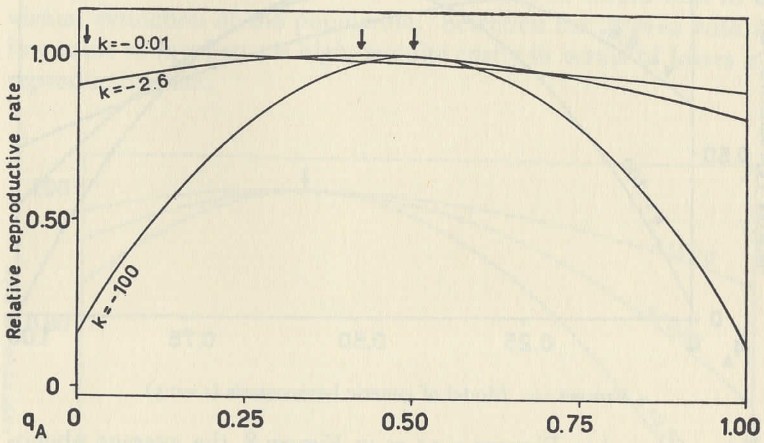

FIGURE 9. Model of genetic homeostasis ($s = 0{\cdot}1$)

First, *k* may be varied holding *s* constant at a lower value than that used in the instance already presented. The particular reproductive rates used for the construction of Figure 9 are:

	$s = 0{\cdot}1$ $k = -0{\cdot}01$	$s = 0{\cdot}1$ $k = -2{\cdot}6$	$s = 0{\cdot}1$ $k = -100$
aa	1·000	1·00	1·0
Aa	1·001	1·26	11·0
AA	0·900	0·90	0·9

The first column represents the case where both *s* and *k* are small; the second where *s* is small and *k* intermediate (equal to that used in the basic model); the third where s is still small while k approaches a very large value. In this last instance, the equilibrium value of q_a is approximately 0·5, which is the limiting value as k increases.

It should be noted that Figure 9 and the subsequent ones are constructed so that the maximum relative reproductive rate for each curve is taken as 1·0. This differs from the scheme of Figure 8, wherein the scale of fitness values was the arbitrary one defined in the text. Values of q_A are given on the abscissa. They correspond to those of q_{Ab} in Figure 8. Should the same magnitudes of X be assumed in Figures 9-11 as in Figure 8, the average phenotypes for X of populations with different q_As can be readily obtained.

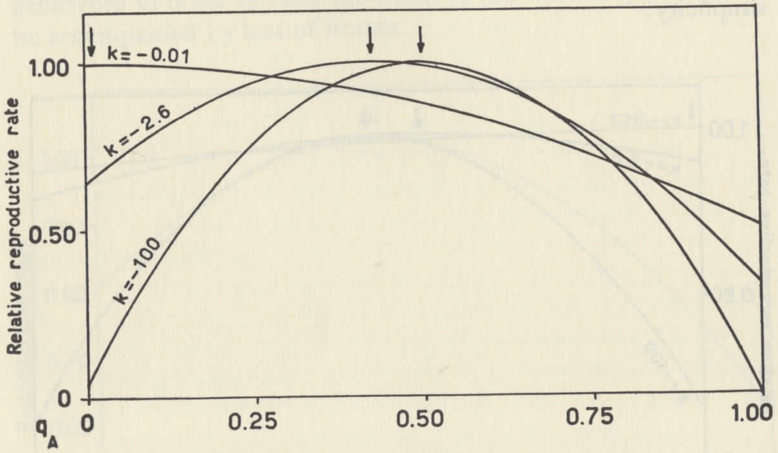

FIGURE 10. Model of genetic homeostasis ($s=0{\cdot}5$)

From Figure 9 it can be clearly seen that the effects of varying k on the shape of the curve are twofold: (1) the equilibrium points of q_A, and with them means of X, are displaced from lower to higher values, with a maximum for the former of 0·5; (2) the peaks are narrowed so that tolerance limits of selection for X are reduced as k increases.

Thus when both s and k are small, it is possible to shift the mean of X a considerable distance without much effect on fitness. With the particular values of the constants used here ($s=0{\cdot}1$, $k=-0{\cdot}01$), fixation of the allele for the maximum value of X is possible at the cost of only 10 per cent in fitness. On the other hand, when k is large, the increase in q_A possible with only a comparable reduction in fitness is from 0·5 to 0·67. Fixation of the desirable allele for X would reduce fitness to 16·7 per cent of the maximum possible.

Figure 10 is analogous to Figure 9 for a high value of s. The relative reproductive rates here are:

	$s=0{\cdot}5$ $k=-0{\cdot}01$	$s=0{\cdot}5$ $k=-2{\cdot}6$	$s=0{\cdot}5$ $k=-100$
aa	1·000	1·0	1·0
Aa	1·005	2·3	51·0
AA	0·005	0·5	0·5

Once more increases in k narrow the peak and the tolerance limits of selection for X. With high values of both s and k, attempts at fixation of the desirable allele for X would lead to a virtual extinction of the population. Selection for X even with a low value of k, when s is high, is quite costly in terms of losses in reproductive rate.

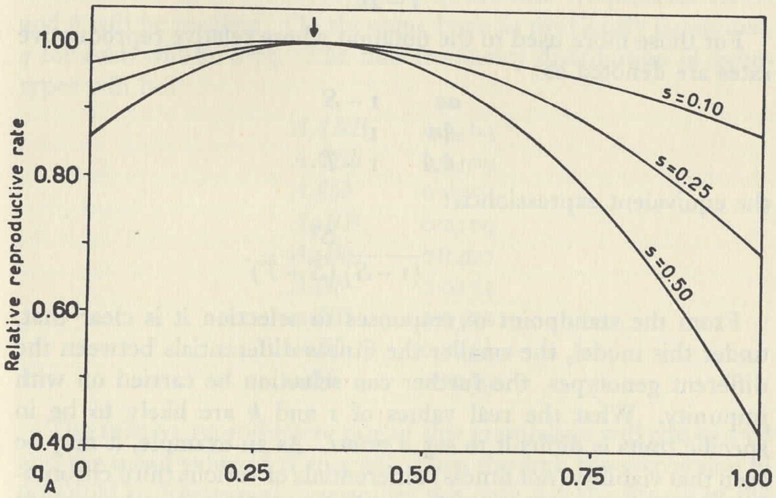

FIGURE 11. Model of genetic homeostasis ($k=-1{\cdot}0$)

Finally, we may consider Figure 11, which shows the effect of variation in s at a constant value of k. The relative reproductive rates here are:

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	$s=0·1$ $k=-1·0$	$s=0·25$ $k=-1·0$	$s=0·5$ $k=-1·0$
aa	1·0	1·00	1·0
Aa	1·1	1·25	1·5
AA	0·9	0·75	0·5

The effects on fitness of increasing *s* here are not as drastic in the region of the optimum, but they become more and more severe as the frequency of q_A is increased.

We can thus see that the power of the homeostatic forces depends on values of *k* and *s*. In general terms, the mean fitness of a population is:

$$q_A^2\,(1-s) + 2q_A\,(1-q_A)\,(1-ks) + (1-q_A)^2.$$

For the point of equilibrium which represents the maximum fitness q_A assumes the value $-\dfrac{k}{1-2k}$. By substitution the maximum fitness is found to be:

$$1+\frac{k^2 s}{1-2k}.$$

For those more used to the notation where relative reproductive rates are denoted as:

aa	$1-S$
Aa	1
AA	$1-T$

the equivalent expression is:

$$1+\frac{S^2}{(1-S)\,(S+T)}.$$

From the standpoint of responses to selection it is clear that, under this model, the smaller the fitness differentials between the different genotypes, the further can selection be carried on with impunity. What the real values of *s* and *k* are likely to be in specific traits is difficult to say *a priori*. As an example, it may be seen that viability (not fitness) differentials of various third chromosome inversions of *Drosophila pseudoobscura* (Dobzhansky, 1947*b*) were found under population cage conditions to have *s* values of 0·12 and 0·14 for larvae from eggs transferred from cages to regular culture bottles, and 0·49 and 0·50 for flies in the population cages. The corresponding values for *k* were −0·71 and −0·75 for the first set of figures, and −0·62 for both of the second.

Under this model the rate at which a plateau is reached is a function of the values of *s* and *k* in addition to being dependent on the parameters specifying the additive effect of gene substitutions. It may also be seen that narrow-peaked curves will present greater discrepancies between gains realized and gains expected on the basis of additive gene action even within tolerance limits. This fact may help to account for various degrees by which selection falls short of expectation on the additive basis. Similarly the asymmetry of the response to selection in opposite directions (e.g. Mather and Harrison, 1949; Robertson and Reeve, 1952*b*; Falconer, 1953) may be due to the asymmetry of the curves of the type represented in our figures.

The question to be considered next concerns the conditions under which a plateaued population can resume response to selection. With the original model and its specific fitness and *X* values assigned to the different genotypes in mind, let it now be assumed that after the population has remained constant for some time, crossovers between *A* and *b*, and *a* and *B* occurred. If no artificial selection for *X* is practised, new equilibrium frequencies for *A* and *b* will be reached. On the same basis as previously computed, *q* for each will be 0·75. The new frequency distribution of genotypes will be:

AABB	0·3164
AABb	0·2109
AAbb	0·0352
AaBB	0·2109
AaBb	0·1407
Aabb	0·0234
aaBB	0·0352
aaBb	0·0234
aabb	0·0039

The relative reproductive rate of this population will rise to 1·08 and the mean value of *X* to 4·50. Thus through the conversion of potential to free genetic variability not only has the fitness of the population increased, but its mean for the trait *X* which was stable at 2·84 gradually rose to 4·50 without any direct artificial selection pressure.

In a selected population whose mean was, as shown, maintained by selection at a little over 3·00, the change in *X* made possible by the release of variation is even greater. With the appearance of *AABB* genotypes in the population it becomes possible to increase their frequency to 1·0 without much sacrifice of fitness. When this process is completed the mean for X is carried to its maximum postulated value of 6, with the relative reproductive rate of the population maintained at 1·0. Relaxation of selection in this new population has, of course, no effect, since only *AB*-carrying chromosomes are now found in it. It is possible that in order to utilize the new genetic variability in this manner it is necessary to have compensation for the loss of heterozygosity at loci *A* and *B* by the origin or increase in the selective advantage of heterozygotes at other loci. Incorporation of such a process into the model would, however, make it too cumbersome for the purposes pursued at this point of the discussion.

It may be seen then that on the basis of the few assumptions made here it is possible to construct a genetic model accounting for observed facts without invocation of new and startling principles. The results obtained by Mather and Harrison (1949) in experiments on selection for the number of abdominal chaetae of *Drosophila* were explained by them in a general manner on the basis of such a model. Perhaps the only addition contributed here is the distinction that the model presented makes between additively genetic control of the traits under selection and the non-additive basis for fitness. This addendum emphasizes the fact that a correlated response in the direction of reduction of fitness is an obligatory consequence of selection for extreme morphological phenotypes. Correlated responses in other properties may be fortuitous, in the sense that they will vary in kind and direction depending on the genetic constitution of the initial population.

The overdominance feature of fitness reconciles the notion regarding predictability of gains in previously unselected populations with the phenomenon of attenuation of realized gains and cessation of progress after a period of selection. The evidence of Lerner and Dempster (1951) from their shank-length selection experiment is in conformity with the properties of the model. It should, however, be emphasized that the latter has been given in a much simplified form. Addition of further loci to the two considered increases the possibilities of releasing free genetic variation. Multiple allelism extends the variety and range of the responses possible. Appearance of new mutations augments the

potentialities for shifting optimum fitness combinations in the direction of the selection pressure applied to *X*. The topography of fitness peaks and valleys for such complex cases becomes multidimensional and not susceptible either to a graphic representation or to simple statistical treatment. The principle, however, remains the same.

18. GENETIC HOMEOSTASIS AND SELECTION

It was noted in the previous section that one of the reasons for differential success in selecting a given character in opposite directions may lie in the asymmetrical shape of the curve relating gene frequency and fitness. There is another and more general reason for this phenomenon. Thus in the hypothetical situation illustrated in Figure 8, artificial selection for an increase in *X* in a population at a mean level to the right of the maximum fitness value for *X* (2·84) will act counter to the direction of natural selection. On the other hand, if selection is attempted for a reduced mean value of *X*, artificial and natural selection will operate synergistically, at least until the equilibrium value of 2·84 is attained.

There are some examples in the literature indicating that the direction of previously applied selection has an effect on the rate of gains (see e.g. Lush's, 1936, analysis cited in section 21, and Dickerson's statement on the results of selection of swine in Craft *et al.*, 1951). However, where no concrete evidence for previous selection in a given direction is available, other interpretations may be more valid. Thus asymmetry may be a matter of scaling, or, in populations of restricted size, it may be related to the confounding of selection and inbreeding effects. For example, in Rokitzky's (1927) study on the number of sternal bristles of *Drosophila*, selection in the low direction apparently led to loss of genetic variability, while selection in the high direction did not (cf. Borissenko's, 1941, study). Similarly, in studies on selection for body weight in mice (Falconer, 1953; Falconer and King, 1953) asymmetry of response was provisionally attributed to inbreeding effects, or at least considered to be related to them.

It should be clear in general that in addition to the antagonistic action of natural and artificial selection, the inbreeding effects, or more generally, departures from the breeding system arrived at in the course of the previous evolutionary history of a given population, may play a decisive rôle in determining the type of selection response obtained (cf. Mather and Edwardes, 1943). Evidence for this is provided by such experiments as those of Shultz (1953) on selection for egg weight in chickens under inbreeding. The increase in homozygosity acted as an added factor determining the genotypic balance and imposed a phenotypic ceiling on high egg weight in the lines selected for this trait. When this inhibiting condition was removed by crossing lines, it was found that cryptic gains had been obtained under selection. Thus selection under inbreeding was effective, but the gains did not manifest themselves on a relatively homozygous background. In other words, gene effects on egg size express themselves in an additive fashion on the phenotypic scale of measurement in balanced (i.e. heterozygous) but not in unbalanced (i.e. homozygous) genotypes. If heterozygosity is indeed an obligate property of a highly fit population, it should be possible to devise appropriate breeding methods to enforce its maintenance in domestic organisms (see Brieger, 1949).

A further consequence of genetic homeostasis is the fact that maximum performance of a population as a whole is not predictable from the maximum performance of an individual. We may use the problem of increasing egg production in the domestic fowl as an illustration. The argument has been advanced that since there are many individual hens that can lay 300 eggs a year, there is no reason why a whole population cannot average this number. The direct statement of this creed is given by Goodale (1950): 'What one bird does, flocks can be bred to do . . .' Presumably the assumption is that the physiological factors limiting the production of any individual are the only ones which limit the production of a group.

However, the laws governing the physiology of populations transcend those governing the physiology of individuals. While it is obviously impossible that the average production of a population be higher than the production of any individuals comprising it, it does not necessarily follow that the population average can ever reach the level of the superior individual. Indeed, not only an *a priori* consideration of the differences in levels of organization but all available evidence refutes this notion.

It is clearly impossible to foretell the selective limit for any trait in a population. Firstly, continuously arising new variability precludes such prediction for individuals. Secondly, the gradual release of potential variability followed by achievement of new equilibria for a population as a whole makes prediction impossible for populations. Nevertheless, estimates of what a temporary ceiling may be for a population performance can be made under some circumstances. For instance, if data on a production-bred flock of chickens indicate that a selection differential of 80 eggs is necessary to maintain a given level of production, the selection limit for the flock is not greater than 285 eggs.

This follows from the fact that the time from ovulation to oviposition is about 24 hours and, as a rule, no eggs are ovulated before the previously formed egg has been laid. Thus maximum individual production per year is 365 eggs, and only hens achieving this figure can be used to replace the flock if, under the conditions specified, an average of 285 eggs is to be maintained.

The temporary nature of this plateau is emphasized. It is entirely possible that mutations or new genotypic combinations could eventually result in a hen producing two or more eggs a day. Obviously this will remove the limitation set. For a whole population it is also not unlikely that an adaptive peak (a new balanced genotype) which will call for a smaller selection differential than 80 eggs for its maintenance can be reached. But barring these two changes, the level of the temporary plateau could be predicted at least in theory for the conditions described. Actually, there are no adequate data for the necessary computations. In the University of California flock (Lerner, 1950; Lerner and Dempster, 1951) for the years 1932 to 1946 the regression of gain on the selection differential is:

$$y = -98{\cdot}2 + 1{\cdot}21 \text{ eggs.}$$

The equation yields a minimum selection differential of 81 eggs for obtaining gains, but this value cannot be taken seriously because:

1. The sampling error is very high.
2. It is not certain that the regression is linear.
3. Other values for the plateau are obtained by diverse techniques of computation.

These include regressions of gain on the production of the dams, on the year of their hatch, on the percent of potential reach, and so forth. Estimates of extinction points of gains, i.e. of flock average ceilings, obtained by these methods range from 200 eggs upwards.

Since averages of over 230 eggs have already been obtained, it is clear that the minimum estimate is in error. What the actual plateau level is cannot be determined with any accuracy from the data. From all of the data available the figure of 260-280 eggs is the one that appears to be the most likely, but of course the evidence for it is not at all compelling. Unfortunately, even the hope that more data will eventually enable an accurate figure to be established has probably no sound basis. The inter-year variation in average production is so great that exceedingly long periods of selection are necessary to arrive at a value within narrow confidence limits. The chances are that, by the time enough information is available, the evolutionary changes within a population will make any estimate obtained obsolete.

These difficulties in no way affect the principle that the population ceiling is lower than the ceiling for individuals in a self-reproducing closed population. Should hybrids between inbred lines be capable of averaging, let us say, 350 eggs, continuous crossing of two inbred populations would produce in each generation a non-self-reproducing population with a mean performance equal to that of the superior individual performance of a closed flock.

As a final point in the present section, the generalization suggested by Mather (1949) that selection advances and variability are different manifestations of the same phenomenon may be recalled. We may restate this principle in a somewhat different form by saying that in successive generations of a closed population the sum of (1) the free variability from heterozygous states of alleles, (2) the potential variability stored in the form of alternative homozygous states of blocks, and (3) the selection changes from complete fixation of certain alleles, is a constant. Migration and mutation introduce a new source of variability originating, so to speak, outside the closed system.

An analogous generalization, admittedly in very vague terms, could be made with respect to fitness and selection advances for economically desirable traits in domestic animals, although it may be impossible to devise a commensurate scale to express this notion symbolically. It seems an attractive idea to postulate a balance sheet for these factors, so that gains from selection in an extreme direction for a given trait must be, in a closed system, paid for by some type of loss. The usual experience, as well as *a priori* evolutionary considerations, suggests fitness as the most likely factor to be penalized. Genetic homeostasis is, of course, a mechanism for balancing the books in a dynamically closed system. Conversion of potential into free variability, or the origin of new variation, changes the closed system into an open one.

The fact that artificial selection for traits useful to man has even now extracted a price in terms of fitness is clearly brought out by Landauer's extensive studies, already cited, on developmental abnormalities. Comparing the incidence of spontaneously occurring, as well as artificially induced, abnormalities in the Jungle fowl and in domestic varieties, Landauer (1948*b*) says:

'Our flock of Jungle fowl is singularly free from sporadically-occurring developmental abnormalities, such as rumplessness, eye defects, beak abnormalities and so forth. This and the very low sensitivity of Jungle fowl embryos to insulin during early stages of development point to the existence of highly effective equilibrating mechanisms in this material. The fact that various mutants show, after their transfer to Jungle stock, a reduced degree of dominance (Fisher, 1935, 1938) may have a similar basis. The many drastic changes, such as great differences in body size, which occurred in the production of the domestic breeds of fowl may well have led to a lowering in the effectiveness of the originally available multiple developmental safeguards.'

Naturally, it cannot be argued from this that the Jungle fowl in competition with domestic varieties would be a more efficient reproducer. Too many other factors enter into the determination of net fitness for this to happen. Nevertheless, it is clear that loss of developmental safeguards has been the toll paid for selection for aims of value to man and not to the organisms subjected to it. Whether this impairment is the result of loss of specific alleles or is due to general increases in homozygosity is a moot point.

19. STABILIZING SELECTION

The rôle of selection in maintaining heterozygosity in populations by means of rejection of deviant homozygous types is an aspect of the subject that has particular significance in the field of breeding. Breeders have tried to accomplish in the course of a few human life-spans what under natural selection may have taken centuries or millenia. Their success in producing differentiation in morphological properties between breeds of dogs, pigeons and other animals has led to a belief that physiological traits underlying economic characters can be as readily modified and fixed. It is not surprising that in their impatience to transform the animal populations under their control, experimenters and practical husbandmen may have, consciously or unconsciously, tended to minimize the fact that they were pitting their short-term efforts against a phylogenetic history extending for many generations.

It must be remembered that until very recent times even the best breeders of animals strove towards the production of superior record-breaking individuals rather than towards the production of superior populations. The former objective, justifiable for racehorse breeding, is in respect of cattle still in the process of replacement by the latter. Even for the faster multiplying chickens the revolution is not nearly as complete as one wishes to believe. In any case, the number of generations bred with group averages in view rather than individual records is still pitifully small, if looked at from an evolutionary standpoint.

The question then arises whether it is reasonable to expect that the reconstruction of a species or variety from the form produced by natural selection, first under feral conditions, and in the last several thousand years under conditions of primitive domestication, could have been accomplished in the course of less than a century. An affirmative answer neglects the existence of genetic homeostasis, and of the conflict between the assumed necessity to inbreed (in order to produce fixation of the desirable traits), and the heterozygosity needed to maintain fitness.

The rejection by natural selection of the extreme deviates is a process referred to by Schmalhausen (1949) as *stabilizing selection* (in one of his usages of the term; see Simpson, 1949). He considers that natural selection is a compound of two phenomena—one directive, and the other stabilizing. The first is the classical form leading to the transformation of a population by shifting its mean properties. The second refers to the tendency of the deviants from the norm to be eliminated. It is based on the idea that survival of the fittest is the survival of the morphologically average.* The diagrammatic illustration in Figure 12, based on a form of representation used by Schmalhausen, may help in visualizing the relationship between the two.

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* 'Survival of the ordinary' was the term used by McAtee (1937), who erroneously believed, on grounds which carry no conviction for population geneticists, that *fittest* and *ordinary* are contradictory epithets.

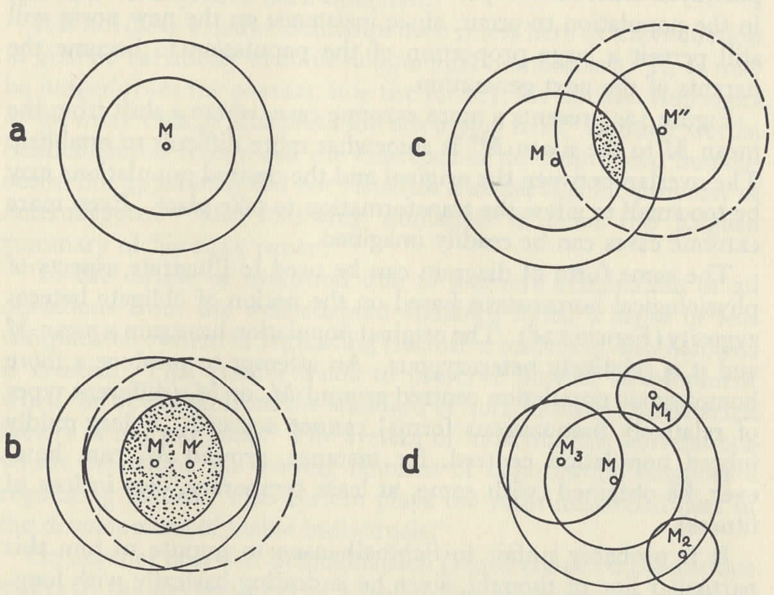

FIGURE 12. Model of stabilizing selection (see text)

The stabilizing form of selection involved in genetic homeostasis may be schematically pictured as follows. Suppose the circle in Figure 12*a* represents a generation of a population with a mean M at the centre. Variation in the population occurs in all directions, the distance of any variant from the mean being proportional to the degree of deviation from it. The inner circle is the area of the norm, individuals in it becoming parents of the next generation. The individuals between the inner and outer circles are deviates rejected by stabilizing selection—they do not contribute offspring to the following generations. These deviates will continue to appear in successive generations, if there is intra-population heterosis based on overdominance.

Let us now assume that the breeder (the agent of directive selection) wishes to move the mean of the population from to M M′. Figure 12*b* portrays this situation. The two smaller circles represent the old norm (with mean M) and the new norm (with mean M'). The dashed circle shows the limit of variability when the new population stabilizes itself around M'. The dotted area is the overlap of the new and old norms. Under the circumstances portrayed differential reproduction may allow the projected change in the population to occur, since insistence on the new norm will still permit a large proportion of the population to become the parents of the next generation.

Figure 12*c* presents a more extreme case, where a shift from the mean M to the mean M'' is somewhat more difficult to establish. The overlap between the original and the desired populations may be too small to allow the transformation to take place. Even more extreme cases can be readily imagined.

The same form of diagram can be used to illustrate aspects of physiological homeostasis based on the notion of obligate heterozygosity (Figure 12*d*). The original population has again a mean M and it is relatively heterozygous. An attempt to produce a more homozygous population centred around M_1 or M_2 (different types of relatively homozygous forms) cannot succeed. A less mildly inbred population centred, for instance, around M_3 can, however, be obtained (with some, at least temporary, cost in loss of fitness).

It is probably unfair to Schmalhausen to impute to him this particular line of thought, since he is dealing basically with long-term evolutionary trends rather than with the problems of artificial selection. Nevertheless, in his brief section on stabilizing selection in agricultural practice, he states rather unequivocally a number of principles with which the concept of homeostasis (both genetic and developmental) is clearly in accord. Thus he says '. . . in most cases natural selection of the most viable organisms is incompatible with artificial selection of the more productive strains.'*

Further: 'Thus it is clear that inbreeding within a single line, which is practised under certain conditions, is entirely ineffective, since the formation of genetic homozygotes drastically diminishes the raw materials with which stabilizing selection operates. Not only is continuous interbreeding necessary for maintaining the diversity of genotypes, but many other methods must be utilized for raising the mutability, even after the advantageous properties of a new variety have been obtained.'

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* Schmalhausen adds: '. . . special breeding and living conditions must be set up in order to raise the vitality of the artificially obtained varieties and races.' This is a very interesting point which falls somewhat outside the limits of this discussion: are the advances in knowledge of nutritional requirements and husbandry practices responsible for relaxation of selection for fitness? Conversely, is the current necessity for prophylaxis, nutritional and other kinds of therapy a payment for increased productivity at the expense of fitness?

It is not clear whether Schmalhausen refers here to the reduction in genetic variability or to developmental homeostasis. If, as may be judged from the context, it is the former, his notions stop short of the more radical interpretation attempted here. In other words, Schmalhausen recognized the existence of developmental homeostasis, but apparently did not visualize it as the specific property of heterozygotes. The following quotation is from the English summary of his 1945 paper:

'In the course of evolution due to a severe elimination of all deviations from the well-adapted standard form, a more or less complicated system of regulating (inclusive buffering) mechanisms is created. This system tends to preserve normal development when the deviation from the standard of both internal and external factors is not too great. The system of morphogenic correlations which determine the leading features of organization acquires a regulating nature. This system plays the most important part in the development of viable individuals.'

On another occasion Schmalhausen (1940) classified the various stages in the development of adaptedness. Interpreting his views in terms of animal breeding, it may be said that introduction of artificial selection under domestication is broadly equivalent to a change in environment. The adaptive values of the different properties of a domesticated organism are no longer based on the contribution that they make to reproductive fitness under feral conditions, which prior to domestication was the basic criterion determining differential reproduction. Not only has the general environment been changed, but many organic weaknesses independent of the details of the external conditions are being sheltered by therapy, dietary supplementation and other artifices.

What is then striven for is what Schmalhausen designates as *allomorphosis*—'an expression of changes in the relationship between the organism and a definite environment, when with the change in the latter and a sufficient plasticity in the organism itself, the latter acquires new adaptations, which correspond entirely to the new condition of the given environment.'

What, however, may occur instead is the phenomenon called by Schmalhausen *hypermorphosis*, when 'a rapid change of the interrelationships between organisms and environment is accomplished by the loss of plasticity of the organism itself, which lags in the tempo of its changes from the changes in the environment.' Hypermorphosis is then the road to extinction of populations. It may be the result of such a radical change in environment that the population lacks the proper kind of genetic reserves to meet it. It may be the effect of reduction in population size, sufficiently great to cause excessive homozygosity, which in turn leads to a breakdown of developmental homeostasis. It is of interest that structures differentiating ancestral species from their successors show high phenotypic variance when they are in the process of degeneration. This may be indeed an example of failure of canalization.

Successful domestication is a matter of allomorphosis. Intensive attempts to improve and fix economic traits, particularly when they are based on close inbreeding, may hover on the brink of disastrous hypermorphosis. A general illustration of this point is given by the high incidence of sterility in domestic animals (see e.g. Lagerlof, 1948) although it must be admitted that the evidence is only suggestive, since we do not know what the fertility levels were prior to the introduction of artificial selection.

A more concrete example, still on the speculative side, is that of the Duchess strain of Shorthorn cattle (Wright, 1923). This family was noted for barrenness, the usual assumption made being that inbreeding accentuated an originally present defect. This interpretation, based on the idea that inbreeding is neutral in its effects, neglects the alternative explanation that sterility was indeed the result of inbreeding. In a pedigree reproduced by Babcock and Clausen (1927) it may be seen that roughly half the females in the family were barren. It is not impossible that specific sterility genes were present in this strain (such as postulated by Mead, Gregory and Regan, 1946, in other breeds of cattle), but hypermorphosis as the explanation of the extinction of the line cannot be dismissed.

The degree to which this effect operates varies from species to species, probably depending on the extent to which artificial breeding practices violate the breeding system determined by previous evolutionary history. Thus, while in chickens it is not uncommon that as many as 80 per cent or more of the zygotes reach maturity, in swine for example only 42·6 per cent of eggs presumably fertilized become pigs at weaning (Phillips and Zeller, 1941), a figure which reaches an even more impressive level when sterile matings are taken into account.

The successful resolution of this difficulty depends on a better understanding of the processes involved. Thus, it may be necessary to reconsider our ideas as to what constitutes the most efficient selection scheme. In the past, the criterion was the gain expected in the trait under selection (e.g. Dempster and Lerner, 1947). If reproductive fitness is also to be taken into account, it is entirely possible that less intensive selection may in the long run be more efficient. Not only can individually valuable alleles be irretrievably lost under high selection intensities, but inbreeding degeneration, appearance of phenodeviants and loss of genetic plasticity can result from too ambitious selection differentials which lead to an excessive restriction of the number of parents in each generation. Improvement at a slower than the maximum possible rate may, on the other hand, allow production of new balanced genotypes concurrently with improvement in the characters selected.

Evidence for the possibility of such reconstruction of new balances is provided by the recovery of fitness at a new level of bristle number in *Drosophila* in the experiment of Mather and Harrison (1949), by the lines of chickens with crooked toes discussed in section 7, and by the experiments on selection under irradiation by Scossiroli (1953), the report on which is currently in preparation. Further examples are found in *Drosophila* studies of Wigan and Mather (1942) and of Buzzati-Traverso (1947). The first referred to selection for the number of sternopleural bristles, as a result of which fertility dropped in the course of successive generations. A high bristle number at this stage of selection was incompatible with normal reproduction. However, at the 10th or 11th generation a recovery in fitness occurred, while the number of bristles continued to rise. Apparently a new genetic constellation leading to a physiologically compatible organization for the new level of bristle number had been built up by the combined action of artificial and natural selection.

An even more instructive illustration is provided by the experiment of Buzzati-Traverso, working with the *aristapedia* mutant. This allele of *spineless* manifested itself in its first appearance in a pleiotropic fashion, the modification of the arista (the last segment of the antenna), which is transformed into a segmented tarsus-like structure, being accompanied by a reduction in length of all six tarsi. The homozygous mutant allele was mass-cultured for three years. An examination of the stock after this period of time revealed the fact that, while the arista modification continued to manifest itself as before, the legs had become entirely normal. It would seem that natural selection of modifiers, made available either by crossing-over or by previous or concurrent mutation, had transformed the genotype of this stock into a more viable form, in which the arista modification could exist without the handicaps it originally imposed on the phenotype for leg length. It is more than likely that had intensive artificial selection for longer legs been applied to the stock, rather than the more gradual pressure of natural selection for fitness, hypermorphosis instead of allomorphosis would have been the result.

An example of an intermediate situation which may be interpreted as a case of potential hypermorphosis arrested by natural selection is given by Taylor's (1946, and unpublished) study of an aberrant comb type in chickens. Transformation of the population was accomplished in this instance only in part, without a homozygous composition having been reached. From a crossbred population in whose phylogeny both rose- and single-comb ancestors were present, Taylor isolated a line in which the sole blade of the single-comb type was replaced by a completely or partially split comb. The frequency distribution of comb types in Figure 13 shows the progress of selection for an increased number of blades. It may be seen that after several generations of selection, the population reached a balanced composition, maintained by artificial selection without further advances after 1946. The genetic basis for multiple combs was found to be complex. Whether this case involves balanced polymorphism or a balanced polygenic system is uncertain. For present purposes, it provides a good example of the operation of genetic homeostasis and of transformation by selection pressure of a heterogeneous collection of genotypes into a genotypically balanced population.

The final example of genetic reconstitution which may be given here is supplied by Sturkie's (1950) study of the naked fowl. Stock carrying the dominant mutant, *apterylosis*, reducing the number of feathers along several plumage tracts, was propagated by mating unselected heterozygous males to normal females. Over a period of 8 generations the viability of heterozygotes to 15 days of age

rose from about 40 to over 50 per cent, while the degree of expression of the defect decreased. In the first two generations some 20 per cent of the chicks showed the extreme form of the trait; in the last two generations under 2 per cent of the chicks fell into this category. Conversely, the frequency of the mildest type of expression increased from 20 to 60 per cent in the period. The parallel to the *aristapedia* case described is obvious.

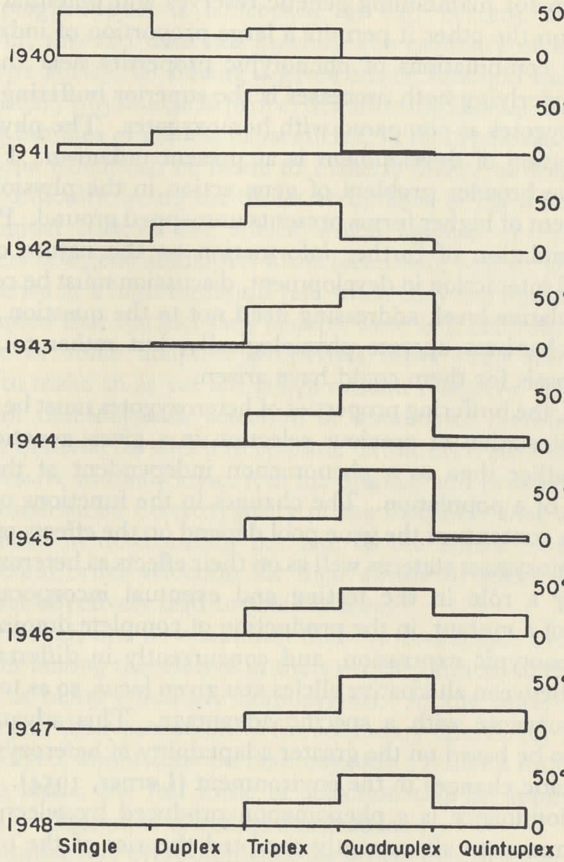

FIGURE 13. Phenotypic composition of a population of chickens selected for multiplex combs (from published, 1946, and unpublished observations of Taylor)

20. EVOLUTION OF BUFFERING PROPERTIES

It is suggested here that heterozygosity has a dual function in the life of Mendelian populations. On the one hand, it provides a mechanism for maintaining genetic reserves and potential plasticity, and on the other it permits a large proportion of individuals to exhibit combinations of phenotypic properties near the optimum. Underlying both processes is the superior buffering ability of heterozygotes as compared with homozygotes. The physiology of canalization of development is at present unknown. For that matter, the broader problem of gene action in the physiology of development of higher forms presents unmapped ground. Pending the accumulation of further information on the nature of gene action and interaction in development, discussion must be confined to a speculative level, addressing itself not to the question of how these mechanisms operate physiologically, but rather to that of how the basis for them could have arisen.

Clearly, the buffering properties of heterozygotes must be viewed as a manifestation of previous selection in a given genetic background rather than as a phenomenon independent of the prior evolution of a population. The changes in the functions of genes and in the contents of the gene pool depend on the effects of alleles in the homozygous state, as well as on their effects as heterozygotes. Both play a rôle in the testing and eventual incorporation or rejection of a mutant, in the production of complete dominance of some phenotypic expression, and concurrently in differentiation of action between alternative alleles at a given locus, so as to endow the heterozygote with a specific advantage. This advantage is thought to be based on the greater adaptability of heterozygotes to unsystematic changes in the environment (Lerner, 1954).

That dominance is a phenomenon produced by selection is a belief common to all currently accepted theories of the origin of this property. Fisher's (1930) hypothesis of selection of dominance increasing modifiers, Haldane's (1930) suggestion that selection operates directly on the primary alleles of varying dominance potency, the physiological hypotheses of selection for a factor of safety in the amount of product of the desirable allele (Plunkett, 1932; Muller, 1932*b*; Wright, 1929, 1934*d*), all share this feature. The experimental observations invoked in support of one or more of these theories (Fisher, 1935, 1938; Harland and Atteck, 1941) appear to confirm the origin of dominance through selection.

Overdominance with respect to the effects of a gene on fitness can arise by selection in a similar way. It is true that when a mutant is a hypomorph or an amorph, so far as its effect on a morphological trait is concerned, it will become a recessive. However, this fact does not preclude the existence of a variety of wild-type alleles, all having a given major function but differing in secondary physiological properties affecting fitness. Recognition of such families of alleles, or isoalleles, in fact removes one of the objections which can be made to Fisher's theory of dominance.

The difficulty facing the direct acceptance of his scheme lies in the original rôle of the alleles which become the dominance modifiers of a gene at another locus (see Lush, 1950). Unless such alleles arise at a high mutation rate when they are needed, it must be assumed that the loci they occupy were in a heterozygous state because of some adaptive properties other than the potential ability to make an as yet not arisen mutant recessive. If these loci were not heterozygous, selection of dominance modifiers would have no material on which to operate. Now, even after the eventually recessive mutants arise, it is the original and primary function which maintained heterozygosity of the modifiers that would still be decisive in determining the fate of the alleles at these loci. The second order selection for their ability to affect dominance could not effectively lead to their fixation.

If, however, one now assumes that the dominance modifiers do not differ among themselves in their primary function, they can be viewed as being *effectively* homozygous. At the same time they may vary in their potentialities for secondary effects, for which the loci involved would thus be heterozygous. When a mutant arises at some locus, the full force of selection can be applied to the secondary differences affecting dominance.

In a similar way overdominance for fitness may originate through coadaptation of secondary properties of so-called major genes. We may consider these as being fixed in a population with respect to their prosthetic parts responsible for the production of major effects in stages of ontogeny far removed from the primary gene products. Each major allelic form may consist of a family of isoalleles differing in secondary subtler properties. Minor imperfections in gene duplication could easily arise and accumulate in a population in a wide variety, thus providing a pool of isoalleles identical in their primary effects and interchangeable. In fact, differences of this order between alleles may indeed be the basis of all polygenic activity.

The situation found by Shultz and Briles (1953) in the blood groups of chickens throws light on this possibility. The original reagents used in their study distinguished two alleles at locus A, which were designated as A^7 and A^9. It was found that artificial selection favoured the heterozygotes A^7A^9 over the homozygotes. Similarly, at locus B heterozygous combinations of alleles B^6, B^{26} and b had a selective advantage, in this case not only under artificial but also under natural selection, Further studies. however, demonstrated that what were assumed to be single alleles were in reality families of alleles, the members of each reacting in a similar way to the original reagents used. Thus an individual classified as a homozygote for A^7, when tested with the reagent A^7, might have been in reality a heterozygote, let us say A^{7a} A^{7b}.

Selection was able to distinguish in this case between families of alleles, but may not have had the power to discriminate between members of each family. We may thus have at each locus a hierarchy of differences of varying magnitude between alleles. The designation of series of multiple alleles as major genes on the one hand, or as isoalleles or polygenic alleles on the other, is a matter of the techniques at the disposal of the observer. The basic fact is that the existence of graded effects of allelic forms appears to be more of a rule than an exception. Exactly which level of difference is selectively significant sometimes may be a relatively easy matter to establish, while at other times it may require methods beyond our present powers, because the selective values depend less on readily discernable morphological than on physiological properties.

It is very probably true that in *Drosophila* the vestigial gene conveys a survival advantage on its carriers kept under exposure to wind by virtue of its phenotypic manifestation visible to the naked eye (L'Heritier, Neefs and Tessier, 1937). It is possible that the inefficiency in mating leading to the lower adaptive value of white-eyed *Drosophila* males (Reed and Reed, 1950) is a direct consequence of the visible change in eye colour. It is much less likely that testis colour in *Ephestia* (Caspari, 1950) is of great selective significance *per se*. Rather it may be an incidental effect of a gene contributing to fitness in an entirely different way, just as it is the higher viability of melanic moths and not their colour

which leads them to displace white forms in certain environments (Ford, 1945). Finally, it is entirely obvious that it is not the arrangement of bands used as a diagnostic for chromosome inversions of *Drosophila* but the physiological properties of the inversion contents that are of adaptive value.

Whether any character seen by the observer is of evolutionary significance as such, or whether it is a fortuitous manifestation of a physiological process undetected by him, cannot be said with certainty. As Mayr (1942) has stated in discussing ecological adaptation, 'A direct selective or adaptational value is not particularly obvious for most of the characters that are subject to . . . . adaptation. We must rather assume that the inheritance of general size or of the degree and kind of pigmentation is correlated with some organ (let us say the thyroid or pituitary) the variation of which is of selective value. It is therefore possible and probable that many of these characters are due to the effects of pleiotropic genes.'

The variety of subtle differences between alleles at a locus (or at contiguous loci) is illustrated, to give a small sample, by the members of the R series in maize (Stadler, 1948), the antigen-controlling genes of cattle (Stormont, 1950), the sex alleles of Habrobracon (Whiting, 1943), the *cubitus interruptus* effects in *Drosophila* (Stern and Schaeffer, 1943), and by the mutation-rate differences in the same species (Timofeeff-Ressovsky, 1932). Their existence, and, where it can be demonstrated, persistence, in populations may be viewed as means of maintaining heterozygosity at obligate levels.

The particular level of obligate heterozygosity for each species and probably for each less inclusive Mendelian population is determined by its evolutionary history. Some species have great morphological variability, others small. In some organisms a considerable degree of inbreeding is possible, in others practically none. A number of the more extreme methods of regulating the level of heterozygosity have been discovered, including the well-known inversions in *D. pseudoobscura* and in *D. subobscura*, and the self-sterility alleles in many plants (East, 1929; Emerson, 1939; Atwood, 1944). Empirical evidence is also available for less stringent methods of enforcement of heterozygosity, as, for example, in alfalfa (Torsell, 1948), but the exact mechanisms operative in these instances are not known.

It is more than likely that a great diversity of mechanisms directed to this end has been developed in different populations. Their precise bases are matter for future investigation. At the same time it should be realized that the principles on which the viewpoint outlined rests have not necessarily received universal support. Indeed strong opposition to them has been expressed.

Thus Muller (1950*b*) has questioned the opinion that heterozygosity can play the important rôle in evolution assigned to it here, on the ground that the general run of mutants must be disadvantageous even in a single dose. He states (italics mine) that 'To suppose otherwise would involve a postulate that a deviant of minor degree is very often better adapted than the normal type. This is improbable except in the case of characters that are still becoming adapted to a condition which is new for the species, in terms of evolutionary time, or, what is much the same thing, to a condition that is local in its incidence on the species. For, except in special cases of balanced polymorphic types, any given character tends to become stabilized at a normal value that is optimal for the long-term conditions, so that only the very rare mutant, even if small in its homozygous effect, will succeed in being advantageous at all. *And where, along the evolutionary track some mutant gene did arise which was advantageous in its heterozygous degree of expression but deleterious homozygously, that gene, though temporarily multiplied as a makeshift arrangement, would usually have become replaced, after a while, by mutant genes of less deviant expression, occupying the same or other loci, which give an equivalent advantage when they were present homozygously.* For such genes would make possible a more uniform and therefore (when all individuals were averaged) a closer approach to the adaptational norm.'

There are some factors which would make this argument less than compelling. Thus there may be limits to what one gene can do. A locus with a neomorphic mutant in a heterozygous state may be responsible for two independent or, more probably, interacting functions, which a single allele may not be capable of performing. In any case, the evidence already presented suggests that balance in populations based on the selective advantages of heterozygotes is a phenomenon extending beyond isolated cases of polymorphism.

It is entirely possible that the evolutionary sequence of events at many loci follows a continual replacement of heterozygotes by homozygotes and *vice versa*. Thus, if at some locus the fixed type is A_1 and a new mutant A_2 arises, which has an advantage over A_1, the population will proceed from

$$\boxed{A_1A_1} \rightarrow \boxed{A_1A_1\ A_1A_2\ A_2A_2} \rightarrow \boxed{A_2A_2}$$

However, if A_2 is superior only in heterozygous form, an equilibrium will be established at the middle step.

Eventually, an allele A_3 may arise which, in a homozygous state will be better than A_1A_2. The population will then go through the series

$$\boxed{A_1A_1} \rightarrow \boxed{A_1A_1\ A_1A_2\ A_2A_2} \rightarrow \boxed{A_1A_1\ A_1A_2\ A_1A_3\ A_2A_2\ A_2A_3\ A_3A_3} \rightarrow \boxed{A_3A_3}$$

The process culminating in the fixation of an allele will show transient trends in gene frequencies. The periods of time between the appearance of mutants superior in homozygous state or of recombinations (if blocks or pseudoallele complexes are involved) will be characterized by constant gene frequencies. These points of equilibrium may be indicated by vertical arrows in the schematic representation of a population history:

$$\underset{(1)}{\boxed{A_1A_1}} \rightarrow \underset{(2)}{\overset{\downarrow}{\boxed{\begin{array}{c}A_1A_1\\A_1A_2\\A_2A_2\end{array}}}} \rightarrow \underset{(3)}{\boxed{\begin{array}{cc}A_1A_1 & A_1A_2\\A_1A_3 & A_2A_2\\A_2A_3 & A_3A_3\end{array}}} \rightarrow \underset{(4)}{\boxed{A_3A_3}} \rightarrow \underset{(5)}{\overset{\downarrow}{\boxed{\begin{array}{c}A_3A_3\\A_3A_4\\A_4A_4\end{array}}}}$$

The population in stage (3) is not in equilibrium. When a population is examined at any other time, only in stages (2) and (5) will this locus contribute to the variance of traits affected by it. In other words, genetic variance in a population at equilibrium can be experimentally observed only when a net heterozygous advantage is present. The exception to this rule may be found in harmful mutants maintained in populations by mutation pressure. These, contrary to our earlier ideas which assigned to them the rôle of genetic reserves, are evolutionary blind alleys with little significance for the successful existence of populations. The main evolutionary process within Mendelian populations is much more likely to be based on the scheme outlined, in which, instead of replacement of one allele by another, the fundamental sequence of events is the replacement of one diploid combination at a locus by another. Such coadaptation on the level of single loci is, of course, accompanied by epistatic coadaptation and integration of longer chromosome segments as suggested by Dobzhansky and by Dubinin.

21. SOME GENERAL CONSIDERATIONS

It is perfectly clear that both the evidence reviewed and the theoretical speculations made can serve only as a framework of the hypotheses itemized in section 2. The considerations brought out in the discussion are basically *ex post facto*, and specific experiments designed to discriminate between the theory expounded here and alternative ones are lacking. For some aspects of it there is an embarrassment of data, and for others only stretches of uncharted territory. That too much information can be a handicap in making generalizations may be a controversial point*. That not enough knowledge makes even first approximation difficult is obvious.

Thus, on the one hand, the disparate evolutionary histories of different species may have led to the development of unique mechanisms for self-regulation of population structure and of individual development, so that the variety of detailed differences between them (as in the data of section 12) obscures what they have in common. On the other hand, mere designation of a phenomenon by the term 'buffering of development' does not imply real understanding of the process; this must await the time when the physiology of gene action and of normal ontogeny is reduced to precise physico-chemical terms. In Landauer's (1952) words, 'It is important that we should not deceive ourselves. Our knowledge concerning the hereditary forces governing normal embryonic development is practically nil.' Only when such great voids have been filled can generalizations of the type attempted here rest on a sound foundation. In the meantime, working hypotheses of some sort are still needed, not only to give direction to future research

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* The Russian biophysicist, Lazareff (as quoted by Gause, 1934), stated: 'For the development of a theory it is particularly advantageous if experimental methods and observations do not at once furnish data possessing a great degree of accuracy and in this way enable us to ignore a number of secondary phenomena which make difficult the establishment of single quantitative laws. If . . . Kepler had had at his disposal the highly precise observations which we have at present then certainly his attempt to find an empirical law owing to the complexity of the whole phenomenon could not have led him to simple and sufficiently clear results. . . . '

but, in a field as closely related to the production of the world's food supply as is genetics, also for practical purposes.

Even if only formal terms are used, there are many problems as yet unsolved which have some urgency for a clearer understanding of the forces governing population structure. As an example, there is the question of maintenance of genetic variability in small populations.

There seems but little doubt that polygenic effects are traceable to integrated chromosome segments. Whether pleiotropic effects of classical genes (or of isoalleles), or specifically acting polygenes in Mather's original sense are involved, is not important. The fact is that delayed responses to selection, such as we have described in section 3, are best accounted for on the basis of block organization. Yet the computed selective advantages of heterozygotes required to maintain the blocks without rapid disintegration must be, as pointed out by Wright (1945), of a higher order of magnitude than is likely, at least under some circumstances.* The question may be stated in a more general way: how many loci can a breeding isolate support in a heterozygous state?

TABLE 20

Percentage of chromosomes in natural populations of *D. willistoni* with detectable recessive effects (Pavan *et al.*, 1951)

	Chromosome II	*Chromosome III*
Lethals and semilethals .	41·2 ± 1·1	32·1 ± 1·4
Subvitals . . .	57·5 ± 1·5	49·1 ± 1·8
Sterility genes . . .	31·0 ± 1·5	27·7 ± 1·6
Retarded development . .	31·8 ± 1·1	35·7 ± 1·8
Accelerated development .	13·7	2·8
Visibles	15·9 ± 2·2	16·1 ± 1·7

In some species the number of genes with deleterious effects in a homozygous state is so large that heterozygosity is ensured by a highly inefficient rate of zygote elimination. Thus the percentage of chromosomes in Brazilian populations of *D. willistoni* which were found by Pavan *et al.* (1951) to have detectable recessive

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* Reference to this point is made by Mather (1953) in his contribution to a recent symposium on evolution. His article and the one by Thoday (1953) in the same volume, which appeared after the present manuscript was completed, contain considerable material bearing on the topics dealt with here.

effects on fitness is so great as to subject homozygotes for any chromosome segment of appreciable length to a tremendous selective disadvantage (Table 20). Now a lifetime egg production by a fruit fly of several hundred fertile eggs allows a considerable margin for elimination of undesirable homozygotes. But in the species which are more economical in their reproductive behaviour the margin for elimination of homozygotes may not be adequate to enforce heterozygosity at more than a limited number of loci.

To take a domestic species as an example, in commercial poultry breeding flocks a hatching season of four weeks may be adequate to maintain a constant population size. In the not uncommon situation in which 15 per cent of the females are selected for reproduction, assuming a rate of 80 per cent daily egg production, at the most (with 100 per cent fertility and 50 : 50 sex ratio) 168 zygotes for every 100 females reaching breeding age are produced. The margin allowed for lethals, semilethals and subvitals is 1·68 to 1. The margin for all unfavourable manifestations, assuming that 15 of the surviving females become parents of the next generation, is 168/15 or 11 : 1.

It is true that for poultry kept under reasonably uniform conditions from generation to generation the range of exploited environments is rather low. Hence variability (including undetectable physiological variation) is not expected to be nearly as great as in flies inhabitating the tropics. Nevertheless, the 10 to 1 margin of elimination (which is an overestimate because of the use of family selection) does not appear sufficient to permit the maintenance of much balanced variability. At the same time the evidence indicates that the genetic variance even in relatively small flocks is not dissipated (Dempster, Lerner and Lowry, 1952), and that balancing mechanisms based on heterozygote superiority are still present in small highly inbred populations (Shultz and Briles, 1953). There is thus a dilemma which it is necessary to resolve without invoking extravagant hypotheses, such as certation, if understanding of the effects of artificial selection is to be advanced, and prediction of consequences of a given breeding scheme made generally possible.

This is not to say that the elaboration of Mendelism and of the principles of population genetics have not led to a partial realization of this goal and thus to progress in the techniques of breeding. It is probably true that much of the genetic improvement in the productive qualities of domestic animals has been achieved prior to the utilization of what we know today as the most efficient breeding methods for selection of additively genetic traits. Yet there is good evidence that the rate of improvement attained today as compared to that of a quarter of a century ago is higher (Lush, 1951). A modern breeder starting from the same genetic level as did his nineteenth century forerunner could without doubt achieve the same progress in a fraction of the time. Whether current breeding methods are adequate to transcend the limits already reached is a subject for debate.

Under the hypothesis of genetic homeostasis, the methods elaborated on the basis of the principles of additive inheritance of quantitative traits (e.g. Hazel, 1943, for pigs; Dempster and Lerner, 1947, for poultry) are applicable to populations relatively unimproved for a desired character. Where selection has led to plateaus, temporary as they may be, these methods, possibly effective in the long run, are not capable of producing immediate results. The *Alice in Wonderland* situation in which 'it takes all the running you can do to keep in the same place' arises when a stationary level of performance can be maintained only by application of the maximum selection pressure possible (at the limit of tolerance on the curve of genetic homeostasis portrayed in Figure 8). A change or reversal of desiderata, on the other hand, may produce immediate effects. An example of the latter situation is provided by Lush's (1936, 1951) analysis of the data from Danish swine-testing stations.

In the early years of selection Danish breeders paid little attention to the thickness of back fat. However, because of a positive correlation (though it cannot be said with certainty that it was genetic) between this trait and characters to which selection was applied, the amount of back fat increased. This is shown on the left side of Figure 14, where an unmistakable trend in this direction can be detected for the years preceding the First World War. The data for the war period were missing but resumption of recording in the 1920s provided evidence that a plateau in back-fat thickness had been reached. Shortly after 1925 definite emphasis on selection for thinner back fat was introduced, and the right side of the figure shows a dramatic response to this selection, continuing for a period of time. The latter years of the period portrayed very probably represent an approach to a new plateau, at which time the problem of achieving further immediate improvement becomes acute.

Textbooks on genetics which devote a chapter to animal improvement as a rule consider the main aim of breeders to be the fixation of desirable alleles (a commendable exception is the recent book by Srb and Owen, 1952). The present discussion should make clear that, barring single genes controlling morphological traits, this is not a tenable view. Homozygosity cannot be the aim of breeding for economically useful characters any more than it is the aim of natural selection. In fact, the basic requirements of a Mendelian population for successful existence is the maintenance of heterozygosity.

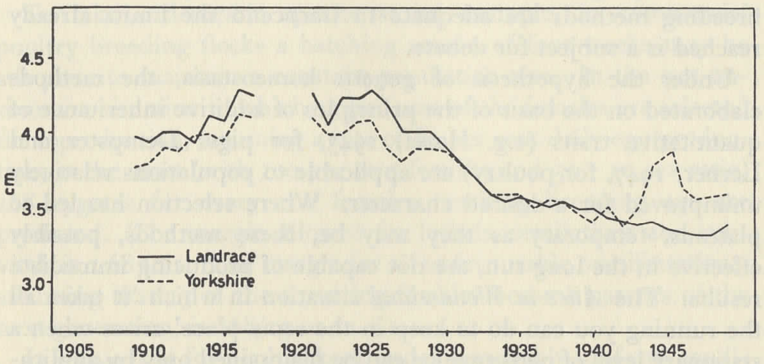

FIGURE 14. Progress of selection for thickness of back fat in swine (Lush, 1936 and 1951)

This fact has been long recognized for populations living in nature, where unpredictable changes and fluctuations in environment necessitate that, behind a uniform adapted phenotype, genetic variability be conserved. Using the terminology of Epling and Catlin (1950), we may say that both *adaptedness*, the attribute of individuals to be fit in the Darwinian sense to their immediate environment, and *adaptability*, the capacity of populations to carry genetic reserves, are required. The thesis here advanced is that the former is mediated by heterozygous advantage in buffering ability as a consequence of which populations become endowed with the latter. The buffering of populations against environmental change (Dobzhansky, 1947*a*) is a by-product of the buffering of individuals. This property of populations emerges from stabilizing selection operating on individuals. Hence, even domestic populations, kept under relatively constant conditions and depending on adaptability only under special circumstances (e.g. epidemics of newly introduced diseases), still possess it.

It is possible that coadaptation of the genetic contents of homologous chromosomes (Dobzhansky, 1948*b*) plays a greater rôle in natural than in domestic populations. In the latter mere diversity of alleles at different loci may provide a sufficient basis for what is usually referred to as heterosis. This is, however, one of the many questions raised rather than answered by the present hypothesis.

There are others, already obvious from previous discussion, that may be asked. There are still others, particularly at the macro-evolutionary level, to which a brief listing cannot do justice. In any case, if the basis of the ideas suggested here is an acceptable one, it follows that the two-dimensional specifications (time and gene frequency) of evolutionary processes used in the early studies of population genetics, necessary as they were to carry us to our present understanding of evolution, will have to be replaced eventually by much more complex multidimensional ones. Even the first crude stages of quantification of the combinatorial properties of genotypes may be beyond our capacity for statistical manipulation. This fact was undoubtedly realized by the pioneers of population genetics, who as a first approximation confined themselves to the simpler forms of analysis. Nevertheless, the pressure for developing techniques of describing not only the gametic gene pool, but also the properties of the zygotic pool of genotypes is becoming increasingly strong. This is brought into relief by the concepts developed by Dobzhansky in his recent publications and by such studies as those of Epling, Mitchell and Mattoni (1953) on natural, and of Wallace *et al.* (1953) on experimental, populations. The first group, finding that fluctuations of frequencies of inversion types in populations of *D. pseudoobscura* cannot always be correlated with environmental changes, suggest that the constant flux of the genotypic compositions of populations is based on polygenic systems such as described for wing venation by Dubinin. The second group, on the basis of irradiation experiments with *D. melanogaster*, find sufficient evidence to believe that the totality of interaction between all components of a genotype forms a more important selection criterion in nature than the additive properties of single genes.

Each genotypic combination may well represent a unique constellation of genes. It is impossible to predict its competitive value under uncontrolled conditions. Nature depends on trial and error and hence needs a wide base of genotypes on which to operate. Error is minimized in successful populations by developmental homeostasis. Genetic homeostasis arises as an after-effect. But the perpetuation of Mendelian populations, whether in nature or under man's control, remains a stochastic process. The purpose of research in population genetics is to gain a better understanding of evolution, which is another way of saying that we seek to narrow the confidence limits of prediction regarding the fate of any population. Similarly, research in breeding must now be directed to more precise studies of population properties, of the forces of genetic homeostasis, and of the methods for overcoming them.

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